Paid Circulation, 35,182

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 252 JUNE 23, 1955 NUMBER 25

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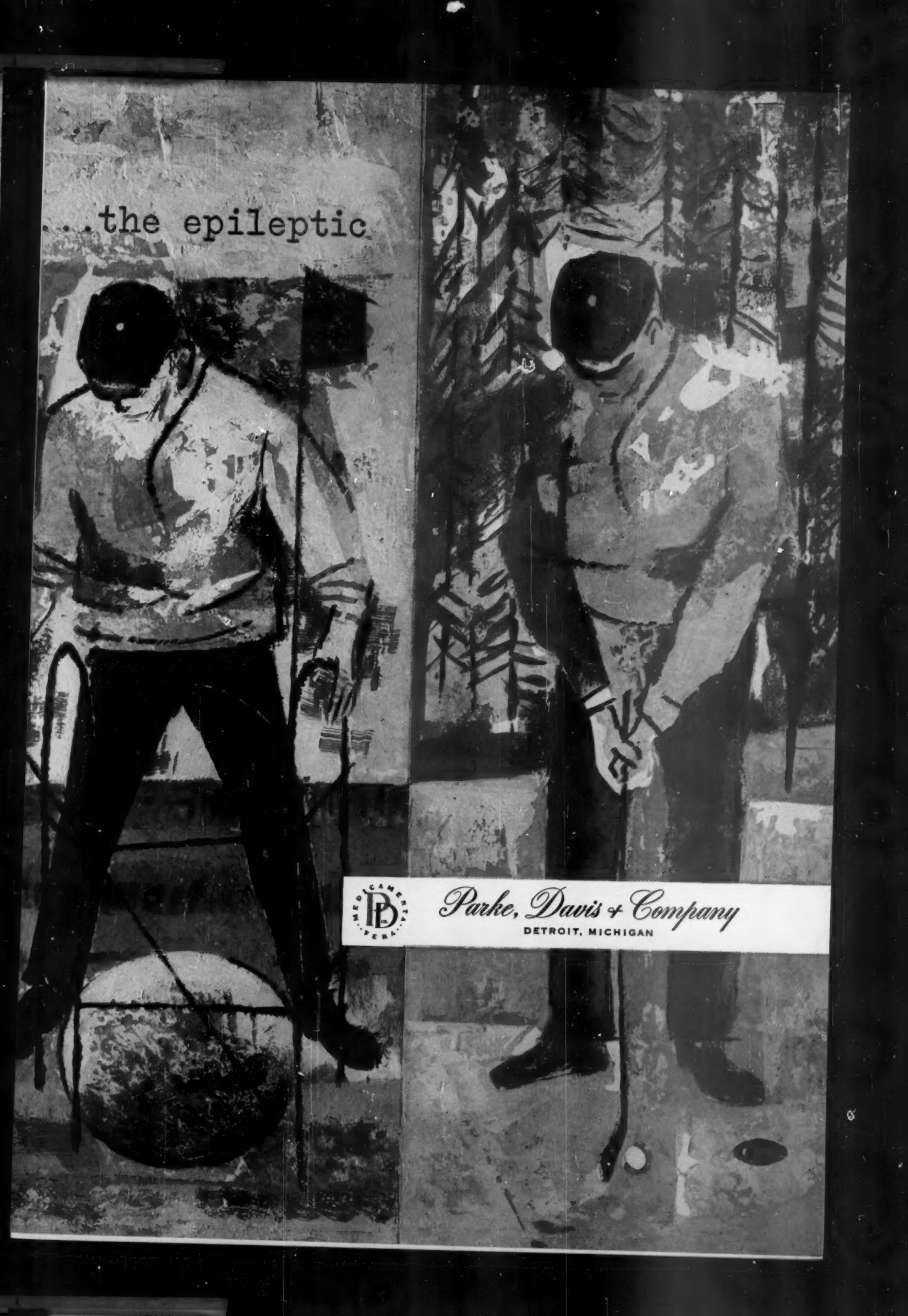
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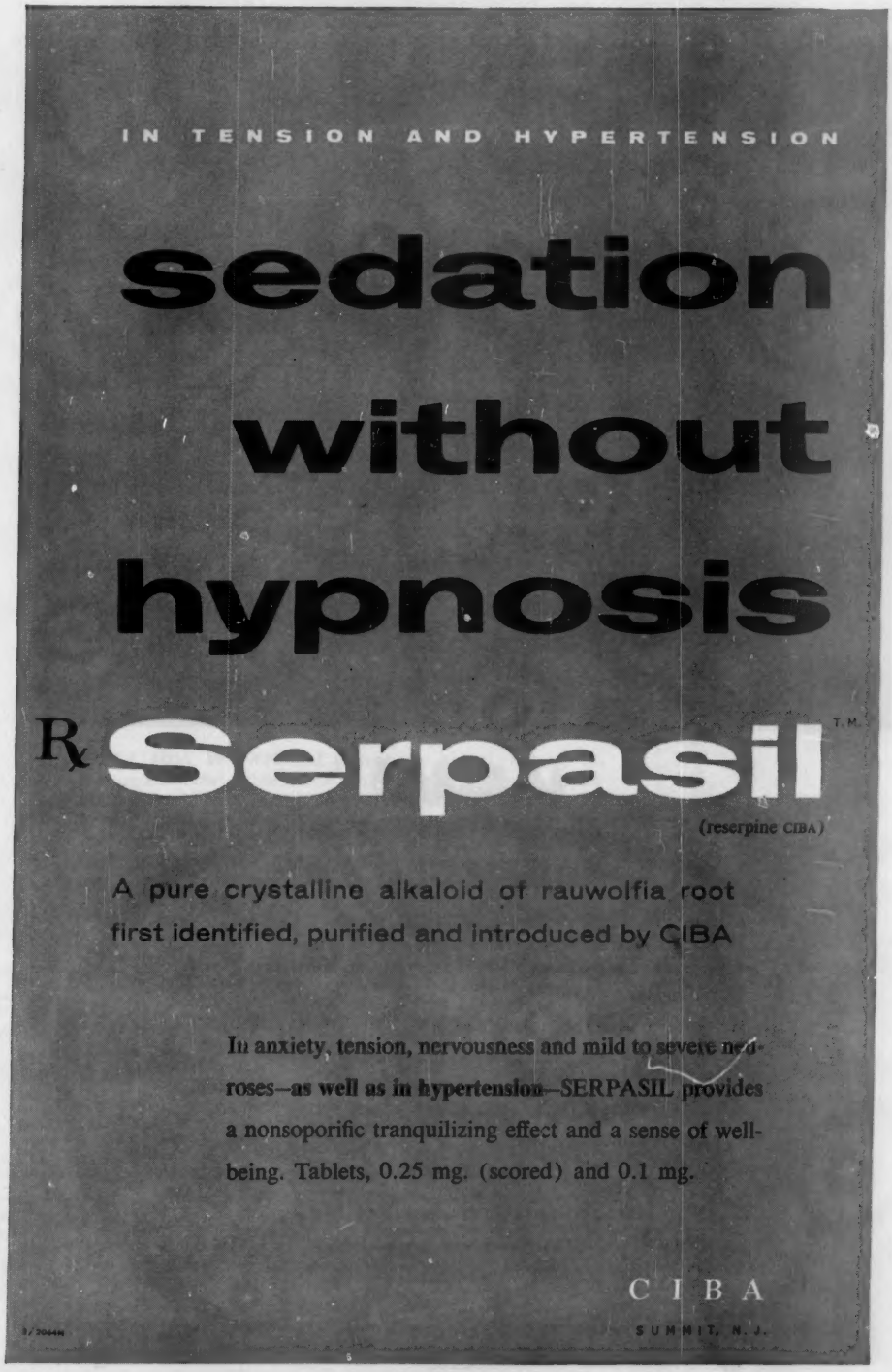
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1. Riseman, J. E. F. and Brown, M. G. Arch. Int. Med. 60: 100, 1937
2. Brown, M. G. and Riseman, J. E. F. JAMA 109: 256, 1937.
3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

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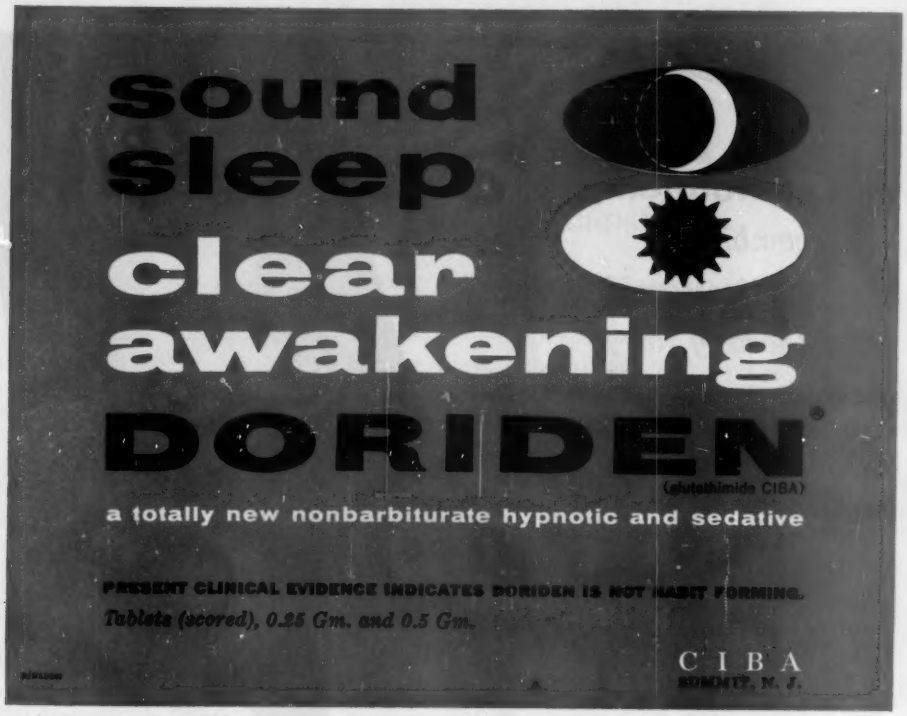

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1. Davis, C. H.: West. J. Surg. 63:53 (Feb.) 1955.

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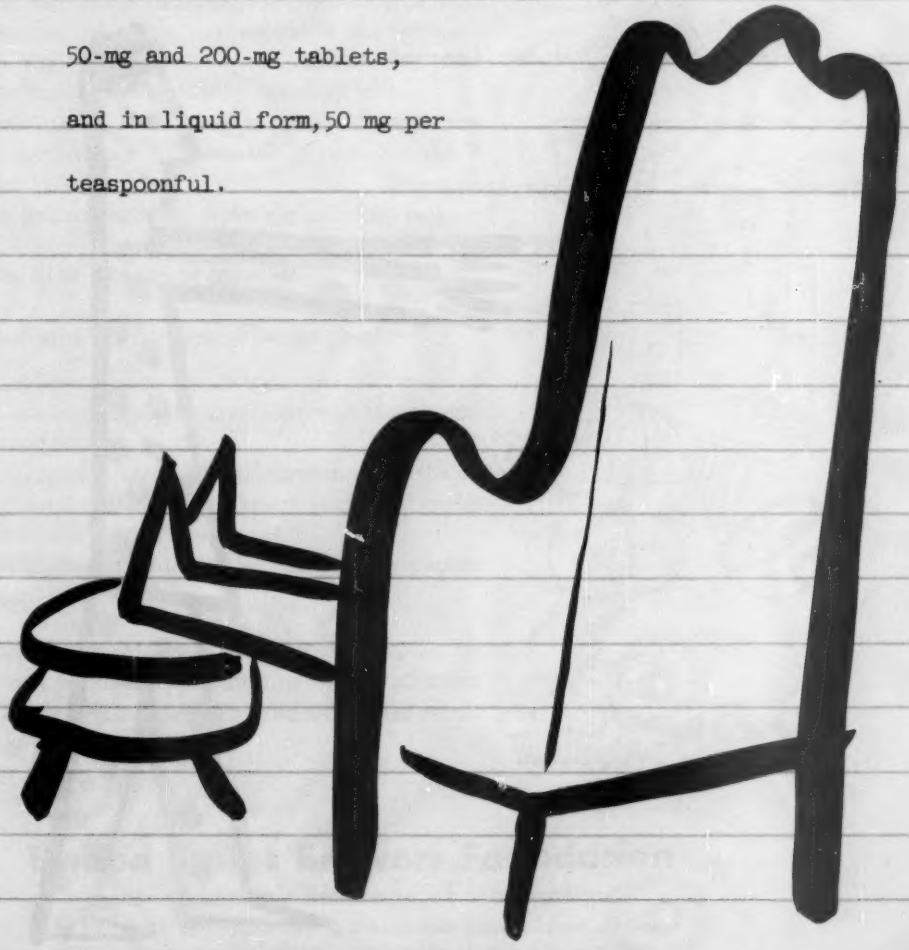

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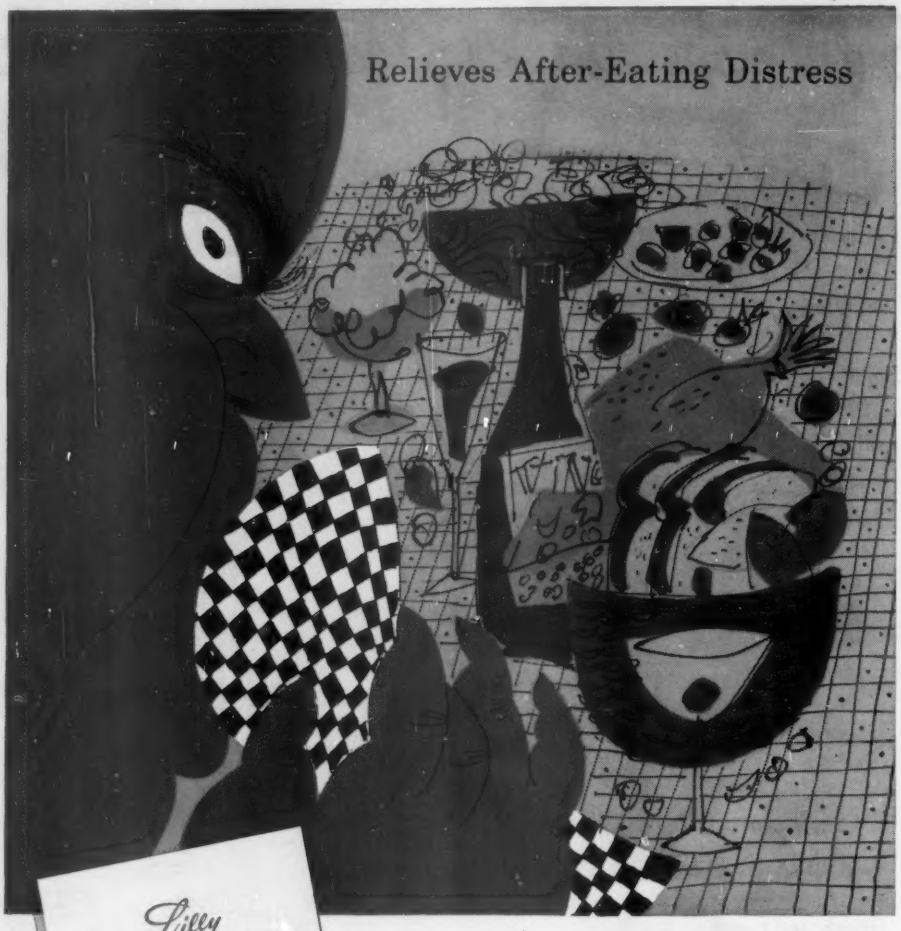

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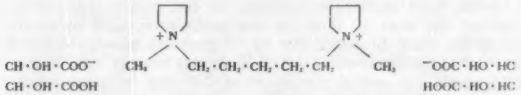
Volume 252 JUNE 23, 1955 Number 25

THE USE OF PENTOLINIUM TARTRATE WITH AND WITHOUT HYDRALAZINE IN THE TREATMENT OF SEVERE HYPERTENSION*

H. Mitchell Perry, Jr., M.D.,† and Henry A. Schroeder, M.D.‡

ST. LOUIS, MISSOURI

PENTOLINIUM tartrate is a pentamethonium derivative in which the two terminal quaternary nitrogen atoms are included in a pyrrolidine ring rather than each being trimethylated:



This substance is an autonomic blocking agent like its parent methonium compound. It is longer acting and has greater absolute effect on blood pressure, coupled with a relatively smaller effect on gastrointestinal motility, than the hexamethonium ion.[1-3]

Pentolinium tartrate has been used alone to lower blood pressure and thereby to permit regression of the signs and symptoms associated with severe hypertension.[4-6] For the malignant phase of hypertension, with its poor prognosis,[7-9] the combination of hydralazine with chemical sympathectomy has offered a lengthened and useful existence.[10] Although in advanced disease vascular damage in the kidney or other vital organs may render a lowered blood pressure potentially lethal, it has always been possible to attain near normotension with sufficiently large and frequent doses of methonium compounds and substituted hydrazine.

In the hope of obviating or ameliorating the annoying side effects of the previous oral administration of hexamethonium chloride, pentolinium tartrate was given by mouth to 30 severely hypertensive patients: 12 had received no previous effective antihypertensive therapy, 12 had shown low tolerance for hexamethonium chloride in combination with hydralazine, and 6 had manifested late toxic reactions to hydralazine after their blood pressure was well controlled by such "combined therapy." Twenty-five of these patients began taking pentolinium tartrate in Barnes Hospital; the others were all in the last two groups and had been studied in detail during prior hospitalizations. The mean age of the entire group was fifty, with a range of thirty-two to seventy-two years; 6 were Negroes, and 13 were females.

Previously Untreated Patients

To 12 patients who had received no prior treatment pentolinium tartrate was given orally six times daily. The initial dose was 20 mg.,§ and every day the individual doses were increased by 20 mg. until there was an appreciable fall in blood pressure. The dose that produced the fall was administered every four hours for any sitting systolic pressure exceeding 140. Half was given for pressures from 130 to 140, and a quarter for pressures from 120 to 130. At this point hydralazine was added in increasing amounts to minimize fluctuations in blood pressure and prevent tolerance to the autonomic blocking agent. Except for the type and amount of autonomic blocking agent given, the technic was exactly that previously found effective,[11] 20 mg. of pentolinium tartrate replacing 125 mg. of hexamethonium chloride.

Of the 12 patients 9 were in the malignant stages of hypertension. All 9 had hemorrhages and exudates in their ocular fundi, and 4 had definite papilledema. All had a high fixed diastolic pressure, and 6 had a mean value over 140. All had laboratory evidence of markedly depressed renal function, with an 11 per cent mean excretion of intravenously injected phenol red in fifteen minutes, and 3 had definite azotemia. Five of the 9 were admitted as medical emergencies in hypertensive encephalopathy or cardiac failure, and of necessity their blood pressures were acutely lowered with parenteral autonomic blocking agents before a base-line value or control laboratory data were obtained. Before entry 2 others had received

*From the Hypertension Division, Department of Internal Medicine, Washington University School of Medicine, and Barnes Hospital.

Supported in part by a grant-in-aid from the National Heart Institute, United States Public Health Service, and the Lasdon Foundation.

†Instructor in medicine, Washington University School of Medicine; assistant physician, Barnes Hospital.

‡Associate professor of medicine and director of Hypertension Division, Washington University School of Medicine; assistant physician, Barnes Hospital.

§Throughout this paper dosages of autonomic blocking agents are expressed in terms of the salt rather than free ion. The only exception is Table 3, where intake is compared with excretion, which can only reasonably be considered as the free cation. The cation comprises 44.5 per cent by weight of pentolinium tartrate and 74 per cent of hexamethonium chloride. The pentolinium tartrate was generously supplied by Wyeth Laboratories, Philadelphia, and the hexamethonium chloride by Burroughs Wellcome and Company, Tuckahoe, New York, and Warner-Chilcott Laboratories, Incorporated, New York City.

250 and 1500 mg. of hydralazine per day. The mean blood pressure of the 9 on admission was 252 systolic, 144 diastolic. The most recent mean monthly blood pressure in the same patients was 153 systolic, 90 diastolic.* Their most recent average monthly intake of pentolinium tartrate was 727 mg., and that of hydralazine 748 mg. per day.* These patients were followed for one to ten months on this therapy (Table 1.)

The other 3 of these 12 patients similarly begun on pentolinium tartrate and hydralazine were in the severe "benign" stages of hypertension characterized by high fixed diastolic pressure and considerable evidence of renal damage, without hemorrhages, exudates or papilledema in the ocular fundi. The mean blood pressure on admission was 194 systolic, 131 diastolic. The most recent mean monthly blood pressure of 141 systolic, 89 diastolic, was effected by an average pentolinium dosage of 415 mg. and an average hydralazine dosage of 306 mg. per day. These patients were followed on this therapy for four to eleven months (Table 1).

The following case report of malignant hypertension illustrates the very high drug intake that may be necessary to achieve normotension in desperate situations.

CASE 1. J.M., a 39-year-old Negro packing-house worker, entered Barnes Hospital in 1950 because of an acute febrile illness thought to be brucellosis; however, he left before definitive diagnosis or treatment was completed. The blood pressure was 150/100, and the urine was normal.

The next admission was in December, 1953, because of dyspnea and precordial pain of 1 year's duration. The blood pressure was 246/148; he was dyspneic and orthopneic, with rales in the bases of both lungs. The fundi had hemorrhages, exudates and papilledema, and cardiomegaly was marked. There was no anemia, but significant laboratory findings included a ++++ test for albumin and microscopical hematuria. The maximum specific gravity of the urine was 1.015. The excretion of intravenously injected phenol red was 18 per cent in 15 minutes; there was no azotemia. Intravenous and retrograde pyelograms were not remarkable; the response to benzodioxane was not abnormal. There was no significant fall in blood pressure after administration of Amytal Sodium. The circulation time from arm to tongue was 32 seconds. Brucella agglutinins were not found.

Oral administration of hexamethonium chloride was begun, and within 3 days the blood pressure was twice recorded as 150/90. Because of nausea, distention and asthenia the patient refused further therapy and was discharged, essentially unchanged, to be followed as an outpatient on a daily dose of 500 mg. of hydralazine and 100 mg. of the crude root of *Rauwolfia serpentina.*

Five months later he entered the hospital as an emergency because of congestive heart failure. He was apprehensive and orthopneic. The fundi again were found to have Grade 4 changes of hypertensive retinitis (Keith–Wagener). Respirations were 30, and there were rales in the lower half of both lung fields, with dullness on the right. The blood pressure was 240/140. There was an irregular apical pulse of 98, with a deficit of 16 at the wrist. As before, the heart was enlarged. There was moderate venous distention; the liver edge was palpable 3 cm. below the right costal margin, and bilateral pedal edema was present. Urinalyses were unchanged except that the excretion of intravenously injected phenol red was only 5 per cent in 15 minutes. The nonprotein nitrogen was 50 mg. per 100 cc. of plasma,† and the red-cell count was only 3,500,000. The venous pressure was equivalent to 215 mm. of saline solution. With morphine, aminophylline and digitalis the symptoms and signs slowly improved, and the patient lost 9.1 kg. Since he continued to refuse combined hexamethonium and hydralazine therapy, he was discharged on digitalis and 1500 mg. of hydralazine and 1 mg. of reserpine a day.

Three weeks later he was again admitted to the hospital as an emergency with considerable respiratory distress, anasarca and oliguria. He had obvious Cheyne–Stokes respirations. The blood pressure was 220/150. The fundi were unchanged except for many fresh hemorrhages. There were rales throughout both lungs, with fluid at both bases. The heart was enlarged, the border of cardiac dullness extending to the anterior axillary line, and there was a regular rhythm with a diastolic gallop and a short blowing diastolic murmur over the aortic area. Hepatomegaly was again noted; there was ascites, with marked bilateral pedal edema. Routine laboratory studies revealed nothing new except a decrease in the red-cell count to 3,000,000 and an increase in the nonprotein nitrogen to 71 mg. per 100 cc. He now agreed to oral pentolinium therapy. The amount was gradually increased to 2500 mg. daily in divided doses. To this was added a maximum of 300 mg. of hydralazine every 4 hours. The blood pressure with the patient sitting fell to 135/95, with moderate asthenia as the major side effect. During the next 10 days he was ambulated, and to assure adequate renal filtration the blood pressure was maintained at a compromise level of 170/110 on an average of 200 mg. of hydralazine and a maximum of 300 mg. of pentolinium tartrate 6 times a day by mouth.

At discharge he had lost 14.5 kg.; there were no further signs of congestive heart failure. The final nonprotein nitrogen level was 27 mg. per 100 cc. Exudate and papilledema were much less noticeable, and there were no fresh hemorrhages in the fundi. Four months after leaving the hospital he was working and felt well; the mean systolic pressure was 155 (he had not learned to take his diastolic pressure), and the mean daily intake of pentolinium tartrate and hydralazine was 929 and 1000 mg. respectively (Fig. 1).

PATIENTS PREVIOUSLY RECEIVING COMBINED THERAPY

For 12 patients receiving combined antihypertensive therapy consisting of hexamethonium chloride and hydralazine, as previously described,[11] the former was replaced by a fifth the amount of pentolinium tartrate. For 10 of them, unpleasant side effects had prevented a sufficient hexamethonium intake; for 2, adequate autonomic blockade had resulted in unusually severe and persistent side effects. Six of these patients were in the malignant, and 6 were in the severe "benign" stage of hypertension. In all the former and half the latter the substitution was made during hospitalization. Each patient remained on approximately the previous constant oral dose of hydralazine four or five times a day and a simultaneously administered variable dose of a ganglionic blocking agent adjusted to give the desired blood pressure. Under such conditions it was possible to compare hexamethonium and pentolinium potencies. On the average a mean daily dose of 2315 mg. of hexamethonium chloride by mouth was replaced by 485 mg. of pentolinium tartrate. With the change in drug the mean blood pressure fell from 173 systolic,

*Since each of the 30 patients considered in this communication takes his own blood pressure in a sitting posture five times a day to gauge the dosage of pentolinium tartrate, the individual monthly pressure and dosage means during treatment are the average of approximately 150 recordings. These individual means are then further consolidated into group means. Similar values cited throughout the paper were obtained in the same manner.

†The maximal normal level of nonprotein nitrogen in the blood after deproteinization by zinc hydroxide as used here[12] is 26 mg. per 100 cc. The low value is due to precipitation of glutathione, ergothioneine, uric acid and perhaps other substances that are not precipitated by the more usual phosphotungstic acid procedure.

102 diastolic, to 156 systolic, 94 diastolic (Table 1).*

Although in general pentolinium tartrate was more effective than hexamethonium chloride in lowering blood pressure because it produced relatively fewer and milder undesirable side effects, it occasionally led to a marked increase in blood-pressure fluctuation that was not controlled by a rearrangement in the dosage schedule. In 2 of the 12 patients the daily variation of systolic pressure in the hospital was regularly 100 to 150. Because of the frequent swings

TABLE 1. *Dosage, Length of Therapy and Blood Pressure, before and after Treatment, for Patients Receiving Pentolinium Tartrate.*

No. of Patients	Status		Before Any Treatment	Previous Situation			Present Situation			Ratio of Pentolinium Tartrate to Hexamethonium Chloride	Duration of Pentolinium Treatment	Average Systolic Deviation	
			Blood Pressure	Blood Pressure	Dosage of Hexamethonium Chloride	Dosage of Hydralazine	Blood Pressure	Dosage of Pentolinium Tartrate	Dosage of Hydralazine			On Pentolinium	On Hexamethonium
					mg./day	*mg./day*		*mg./day*	*mg./day*		*mo.*		
Initial therapy, pentolinium tartrate and hydralazine:													
9	Malignant hypertension:	Mean	252/144				153/90	727	748		6.1		
		Range	203–300				106–167	206–1239	250–1000		1–10		
			120–170				111–73						
3	Severe "benign" hypertension:	Mean	194/131				141/89	415	306		7.3		
		Range	186–201				128–150	121–714	125–625		4–11		
			125–135				85–98						
Present pentolinium tartrate therapy because of side effects with hexamethonium:													
6	Malignant hypertension:	Mean	245/141	178/103	2470	625	162/94	568	560	0.23	6.8	20	18
		Range	190–276	155–222	600–4500	75–1000	140–178	134–600	0–1000	0.07–0.33	4–9	15–34	13–23
			120–160	79–144			84–115						
6	Severe "benign" hypertension:	Mean	212/122	168/101	2159	569	149/94	401	449	0.19	7.6	16	16
		Range	190–240	130–187	750–2450	400–750	130–160	60–785	250–750	0.08–0.32	2–11	14–21	12–21
			105–150	80–115			80–115						
Present pentolinium tartrate therapy because of hydralazine toxicity:													
2	on hydralazine therapy:	Malignant hypertension	230/140	162/92	3255	500	160/80	120	100	0.04	10	14	14
		Benign hypertension	200/101	175/85	2309	750	145/75	300	250	0.13	10	17	14
2	on reserpine therapy:	Malignant hypertension	210/135	167/92	1000	342	156/93	310	—	0.31	12	25	23
		Benign hypertension	242/118	175/85	1330	500	170/85	300	—	0.23	8	19	15
2	on sodium azide therapy:	Malignant hypertension	250/150	142/91	2497	500	169/98	1242	—	0.50	4	26	8
		Benign hypertension	238/120	157/80	2003	750	177/92	954	—	0.48	11	27	11

*That the patients in the malignant stages needed considerably less pentolinium tartrate than the 9 similar patients in the preceding group may be correlated with the stage of therapy, the latter having just begun treatment and some of the former having taken drugs sufficiently long to be needing somewhat less ganglionic blocking agent than was necessary initially.[3]

between hypotension and extreme hypertension, hexamethonium chloride was reinstituted, with some increase in mean blood pressure but with marked diminution in daily systolic variation, in 1 case to less than 25. In another patient of this group marked fluctuations were present but did not make it necessary to discontinue pentolinium. The vasomotor instability was most evident initially and when mean blood pressure had been poorly controlled with hexamethonium chloride but was lowered with pentolinium tartrate.*

12 patients considered in this group. On hexamethonium chloride the average systolic deviations varied from 12 to 23 mm. (mean 16); on pentolinium tartrate the corresponding extremes were 14 and 34 (mean 18). Similarly, average diastolic deviations varied from 6 to 12 (mean 9) on hexamethonium chloride and 6 to 17 (mean 10) on pentolinium tartrate. Obviously, neither the lower limit nor the average of the deviation was different for the two drugs. The only definite difference was in the case reported below, in which the average monthly systolic

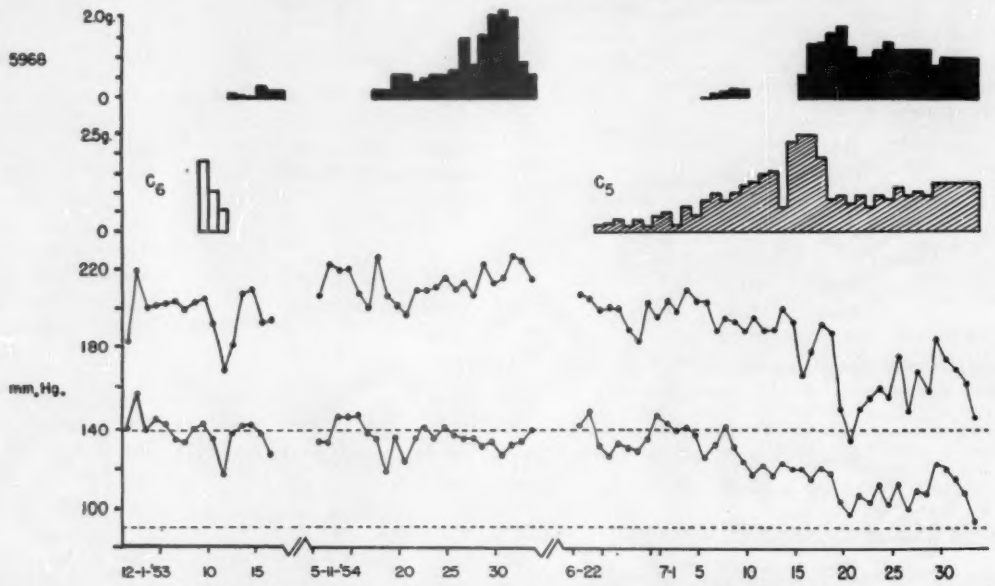


FIGURE 1. *Medication and Blood Pressure As a Function of Time in Case 1.*

The bar graph represents drug intake. Hydralazine (5968) is black, hexamethonium chloride (C_6) is white, and pentolinium tartrate (C_5) is crosshatched. The line graph represents blood pressure. The solid dots indicate systolic, and the open dots diastolic pressure. Each dot is the average of at least six pressures taken in the sitting position by nurses every day. Three separate hospitalizations are indicated by breaks in the time line. Between the first and second admission the patient was taking 100 mg. of the crude root of R. serpentina *and 500 mg. of hydralazine a day. Between the second and third admissions he was taking 1 mg. of reserpine and 1500 mg. of hydralazine a day.*

The average deviation from mean blood pressure was calculated in an attempt to quantitate vasomotor instability. For 5 patients who changed ganglionic blocking agents at home, the effect of the two drugs was determined under identical conditions and without any time lag. During the month before and after the change in medication both the mean pressure and the average deviation were calculated for each patient separately. Included among these 5 patients were the 2 who could not tolerate pentolinium tartrate in the hospital; they later tried it at home, where it again produced marked systolic fluctuations. For the other 7 in the group the month before and the month after hospitalization were similarly compared. A total of 3360 sitting pressures were used for the variation increased from 14 to 26 in the hospital and 14 to 34 at home with the substitution of pentolinium tartrate for hexamethonium chloride. The corresponding increases in average monthly diastolic variations were from 8 to 16 and from 10 to 18. Two other patients had suggestive increases in systolic variation from 15 to 20 and from 17 to 21 with the change in blocking agent; however, there was no corresponding instability in diastolic pressure. The other 9 patients showed no more than a 2-mm. difference in average systolic or diastolic deviation with the change in drugs (Table 1).†

The following case concerned one of the patients alternately given hexamethonium chloride and pentolinium tartrate, with a decrease in mean blood pres-

*For 3 patients of the 12, in the previously mentioned group whose therapy was begun with pentolinium tartrate, systolic fluctuations were striking, causing hexamethonium chloride to be substituted in 1. When this man tried pentolinium tartrate again at home the average systolic deviation rose from 12 to 24.

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sure and a concomitant marked increase in daily fluctuations with the latter:

CASE 2. R.P., a 40-year-old farmer, was asymptomatic in 1946 although he was found to have a blood pressure of 190/130 with questionable cardiomegaly and Grade 1 changes of hypertensive retinitis (Keith–Wagener). At that time a trace of albuminuria was found. Intravenous pyelography was not remarkable. There was no azotemia; 30 per cent of intravenously injected phenol red was excreted within 15 minutes, and an electrocardiogram was within normal limits. No treatment was instituted.

Early in 1953 failing vision, paroxysmal nocturnal dyspnea and nocturia were noted. Exertional dyspnea and pedal edema appeared within 6 months. In May, 1954, he entered Barnes Hospital with normal vital signs except for a blood pressure of 250/164. Fundoscopic examination revealed hemorrhages and exudates, with blurring of the disk margins but without definite papilledema. The lungs were clear except for rare rales at the right base; the heart was enlarged, the border of cardiac dullness extending to the left anterior axillary line, without murmurs, gallop or arrhythmia. The liver edge was palpable 4 cm. below the right costal margin, and there was marked pedal edema. Urinalysis showed a +++ test for albumin, with microscopical hematuria. The hemogram was normal except for a white-cell count of 14,000, with some shift to the left. The nonprotein nitrogen was 37 mg. per 100 cc.; 15 per cent of intravenously injected phenol red was excreted within 15 minutes. The circulation time was 45 seconds from arm to tongue, and the venous pressure was equivalent to 228 mm. of saline solution.

During a week of bed rest in the hospital the average blood pressure, as taken by the nurses with the patient supine, was 248/163. He was therefore begun on increasing doses of oral hexamethonium chloride, which lowered the mean blood pressure to 202/123 in 10 days. Hydralazine was then added in increasing doses. Nevertheless, after a month in the hospital, he was taking 1.0 gm. of hydralazine and 3.0 gm. of hexamethonium chloride by mouth each day to maintain a blood pressure of 207/127. At this point 1.0 gm. of pentolinium tartrate per day in divided doses was substituted as the ganglionic blocking agent; hydralazine was continued without change. On this regimen the mean blood pressure temporarily fell to 181/106; however, systolic fluctuations of over 100 and diastolic fluctuations of over 75 within 4 hours became frequent. After 17 days of rearrangement of the pentolinium dosage schedule in an unsuccessful effort to level out the blood-pressure curves, hexamethonium chloride was reinstituted in approximately the previous dosage, resulting in a high but relatively nonfluctuating blood pressure, with a mean value of 217/136 for the final 11 days of hospitalization.

After discharge at the patient's request drug intake declined, and the blood pressure rose. Oral administration of pentolinium tartrate was therefore begun again. On 300 mg. 4 times a day the mean weekly pressure fell to 160/87. Five months later he was taking an average of 0.85 gm. of pentolinium tartrate and 1.00 gm. of hydralazine per day, with a mean blood pressure of 157/93. Asthenia and occasional hypotensive episodes persisted, but constipation, dry mouth and difficulty with vision had decreased. By then the average variation in systolic pressure from its mean value was 30 mm. This figure was 26 immediately after administration of pentolinium tartrate was begun for the 1st time and 34 immediately after the 2d attempt with this drug. Just before hexamethonium chloride was discontinued the figure was 14 mm. on both occasions (Fig. 2).

PATIENTS WITH DELAYED TOXICITY FROM HYDRALAZINE

In 3 patients originally in the malignant and 3 in the severe "benign" stages of hypertension, whose average blood pressure before treatment had been 231 systolic, 131 diastolic, and who had been well controlled with hexamethonium chloride and hydralazine by mouth, collagen disease developed.[14-16] Before this complication the mean blood pressure on therapy had been 163 systolic, 88 diastolic, and the mean daily intake had been 2063 mg. of hexamethonium chloride and 557 mg. of hydralazine. With the advent of this syndrome the mean blood pressure fell to 142 systolic, 79 diastolic, despite a reduction in average hexamethonium chloride dosage to 778 mg. and in hydralazine dosage to 276 mg. per day.

Only the 2 patients with the mildest and least typical symptoms of collagen disease continued to take even small amounts of hydralazine, and the intake was diminished to a third and a fifth of the previous

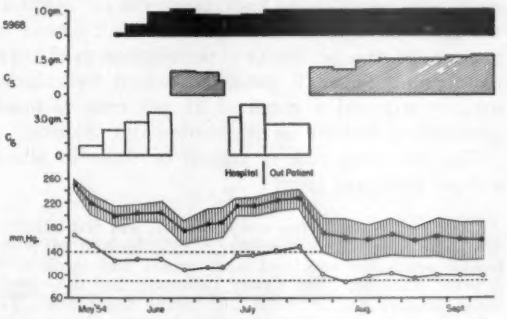

FIGURE 2. *Medication and Blood Pressure As a Function of Time in Case 2.*

The conventions are the same as those in Figure 1, with the addition that the vertical crosshatching indicates the average daily deviation in systolic pressure. The decrease in mean blood pressure and the accompanying increase in average systolic deviation during pentolinium therapy is evident. Blood pressures were all measured in the sitting position six times a day by nurses in the hospital and five times a day by the patient at home.

optimum level. To this were added small amounts of pentolinium tartrate as the ganglionic blocking agent. The result was better control of blood pressure than previously (Table 1); moreover, the arthritides, which had been the major complaint, lessened markedly.

In 2 patients with moderately severe manifestations of delayed hydralazine toxicity the offending drug was discontinued, with regression of the stigmas of multiple-system disease. Treatment was then attempted with reserpine in addition to relatively large amounts of pentolinium tartrate in place of hexamethonium chloride. Here, the previous degree of control was approximated (Table 1).

In the 2 patients with the most acute manifestations of delayed hydralazine toxicity, the drug was discontinued, with rapid disappearance of the evidence of collagen disease and a quick return to hypertension. Sodium azide,[17] in increasing doses up to 1.25 mg. five times a day combined with very large amounts of pentolinium tartrate, could not control the blood pressure adequately (Table 1). The mean blood pressure does not fully indicate the failure of control because a variable systolic pressure has re-

placed a stable one. Of the 6 patients considered these 2 had originally obtained the best response to therapy; their blood pressures had been lower and more stable, and, moreover, they had lost all the original unpleasant side reactions to the treatment.

It is interesting to note the fourth column from the right in Table 1, in which the pentolinium and hexamethonium intakes are compared. The pair of patients who continued with small amounts of hydralazine obtained improved control of blood pressure with an average of less than a tenth as much pentolinium tartrate as their previous dose of hexamethonium chloride. On the other hand the 4 patients who discontinued hydralazine did not maintain the previous level of blood pressure with almost 40 per cent as large an intake of pentolinium as of hexamethonium. The 12 patients without hydralazine toxicity required a mean of 21 per cent as much pentolinium tartrate as hexamethonium chloride.

The following case is typical of those in which sodium azide was given.

CASE 3. I.W., a 32-year-old housewife, was first admitted to Barnes Hospital in February, 1953, because of severe frontal headaches associated with nausea and vomiting of 2 years' duration. The history indicated that the systolic blood pressure had exceeded 240 during this period. The sole other symptom was nocturia for 5 years. On entry she was in no distress, and the vital signs were normal except for a blood pressure of 251/152. Hemorrhages, exudates and papilledema were seen in the ocular fundi. The lungs were clear to percussion and auscultation. The heart was enlarged, the border of cardiac dullness extending 10.5 cm. to the left of the midsternal line; a precordial systolic murmur was noted, but no gallop was heard. There were no abdominal masses and no tenderness. Pedal edema was not present. Urinalysis revealed a ++ test for albumin and microscopical hematuria. The nonprotein nitrogen was 31 mg. per 100 cc.; 7.5 per cent of intravenously injected phenol red was excreted in 15 minutes. Combined therapy with hydralazine and hexamethonium chloride orally every 4 hours resulted in a temporary drop in blood pressure to 120/75 for several days, with a concomitant rise in nonprotein nitrogen to 41 mg. per 100 cc. After 3 weeks in the hospital the albuminuria had diminished to only a trace, the blood pressure averaged 145/95, and the azotemia had entirely disappeared. The patient was discharged on a dosage schedule calling for 100 mg. of hydralazine and a variable amount — up to 500 mg. — of hexamethonium chloride every 4 hours, depending on the blood pressure in the sitting position.

She remained entirely symptom free, and the mean weekly blood pressure varied between 138/89 and 144/95 for 7 months, when a definite drop of about 20 mm. in both systolic and diastolic pressures occurred and persisted despite the halving of both the hexamethonium and the hydralazine intake. The insidious onset of anorexia was noted at about this time. Two months later severe swelling and pain in the joints of the hands appeared within 5 days. After a week of severe arthritic symptoms the temperature in the outpatient department was recorded as 102.2°F., and the blood pressure as 120/70; a tender liver edge was palpable. The white-cell count was 4000. The nonprotein nitrogen was 41 mg., and the globulin was 2.8 gm. per 100 cc. The cephalin-cholesterol flocculation was ++++, and the corrected sedimentation rate was 54 mm. per hour. In the peripheral blood many cells typical of lupus erythematosus were found.

Since the abnormal signs, symptoms and laboratory findings persisted despite reduction of the hydralazine to 125 mg. per day, the patient was readmitted to the hospital in May, 1954. The vital signs were within normal limits except for a blood pressure of 192/104. There was no objective evidence of arthritis, although she complained of pain. No hemorrhages or exudates were seen in the ocular fundi, and the disks appeared normal. The lungs were clear to auscultation. Cardiomegaly was unchanged. The cervical lymph nodes were enlarged; a tender liver edge was felt 3 cm. below the right costal margin, and the spleen was easily palpable. There was no edema. The red-cell count was 3,600,000, and the white-cell count 5400; a +++ test for albumin and microscopical hematuria were found. The nonprotein nitrogen was 29 mg. per 100 cc., and the excretion of intravenously injected phenol red was 10 per cent in 15 minutes. Cephalin-cholesterol flocculation was ++++, and the thymol turbidity was 13.5 units. A smear of peripheral blood continued to show a great many cells typical of lupus erythematosus. Hydralazine was discontinued, and a substitute (Ba 13050) was begun. The patient complained of a definite increase in joint pain within 72 hours, and tender indurated subcutaneous nodules appeared. Because symptoms were increasing and control of the blood pressure had not been achieved this drug was stopped after 8 days. Simultaneously, hexamethonium chloride was replaced by pentolinium tartrate, on which the mean blood pressure fell considerably but daily fluctuations increased. Increasing oral doses of sodium azide were begun as a substitute for hydralazine, without any effect. After taking pentolinium tartrate for 3 weeks she requested hexamethonium chloride again before being discharged. A definite rise in both systolic and diastolic pressure followed, accompanied by a decrease in fluctuation.

Because of the steadily mounting hypertension she was persuaded to try pentolinium tartrate again at home. The result was a dramatic fall in mean blood pressure, coupled with a doubled average systolic deviation from this mean (Table 2 and Fig. 3).

RENAL EXCRETION

Urinary pentolinium recovery was measured in 2 patients with dual objects in mind. The first was to compare the percentage of ingested hexamethonium and pentolinium ions that was excreted renally. The second was to compare the amount of pentolinium put out by the kidney after parenteral as opposed to oral administration.

The principle of pentolinium assay involved the precipitation of a water-insoluble reineckate, its solution in acetone and mensuration of the resultant red color.[12] The method was essentially the one previously used for hexamethonium assay in urine.[13] The only variation was necessitated by the low solubility of pentolinium reineckate in acetone. The aliquot of urine was limited to one containing less than 0.1 millimol (23.9 mg.) of pentolinium ion so that all the corresponding reineckate could be dissolved in five successive 20-cc. portions of acetone, which were then pooled and read at a wave length of 525 millimicrons on the Beckman spectrophotometer. Under these conditions it was found that an optical density of 0.200 was equivalent to a 0.94-millimol concentration of either methonium ion—0.094 millimols per 100 cc. of acetone (Fig. 4). The necessarily low optical density of the solution of pentolinium in acetone exaggerated technical errors only slightly so that recovery of known amounts of the drug added to normal urine approximated that previously reported for hexamethonium ion.[13]

The first patient was a thirty-seven-year-old physician with severe benign hypertension. In the hospital mean pretreatment blood pressure at rest in the

supine position was 201 systolic, 133 diastolic. Hexamethonium chloride was given in increasing doses for nine days, when it was replaced by pentolinium tartrate. Hydralazine was instituted, and the dose increased stepwise according to the usual scheme[11] without regard to the change in autonomic blocking agent. With inception of therapy the blood pressure promptly fell to approximately 180 systolic, 120 diastolic, where it remained for a week, finally falling to normal levels after a fortnight. The hexamethonium recovery was in the usual range,[13] approximating 5.3 per cent of the daily oral intake, whereas

TABLE 2. *Mean Blood-Pressure and Systolic Fluctuation in Case 3.**

PERIOD	DOSAGE OF HEXAMETHONIUM CHLORIDE	DOSAGE OF PENTOLINIUM TARTRATE	DOSAGE OF HYDRALAZINE	DOSAGE OF BA 13050†	DOSAGE OF SODIUM AZIDE	BLOOD PRESSURE	AVERAGE SYSTOLIC DEVIATION‡
	mg./day	*mg./day*	*mg./day*	*mg./day*	*mg./day*		
1st hospital admission (early)	896					214/132	20
1st hospital admission (late)	1280		490			138/88	15
6 mo. after discharge (good control)	2240		500			144/94	8
1 yr. after discharge (collagen disease)	464		125			124/74	5
2d hospital admission (early)	1900			437		183/107	10
2d hospital admission (middle)		508			2.07	146/96	22
2d hospital admission (late)	2330				3.91	172/107	10
2 wk. after discharge	5000				5.00	194/114	13
10 wk. after discharge		1270			6.25	161/100	26

*Every figure mean for representative wk., each value being consolidation of 35 recordings, except for *2d hospital admission (late)*, which represents entire 3-day period of hospitalization after hexamethonium chloride restarted.

†Sulfur-containing pyridazine substitute for hydralazine.

‡Simple measure of daily blood-pressure fluctuation, equaling mean difference between individual readings and average value.

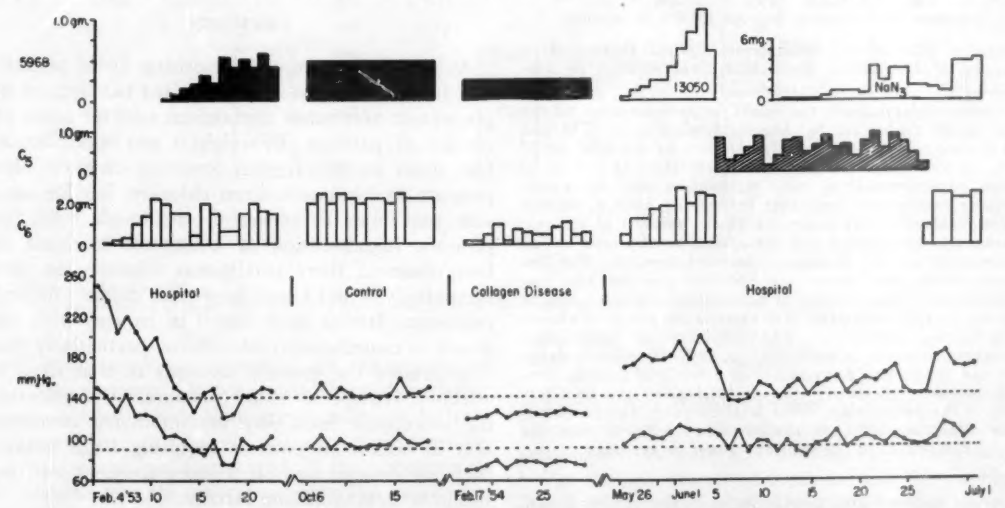

FIGURE 3. *Medication and Blood Pressure As a Function of Time in Case 3.*

The conventions are the same as those in Figure 1, with the addition of two drugs, both shown as open bars containing a designation. The number 13050 indicates a trimethylated, sulfur-containing pyridiazine derivative, and NaN_3 indicates sodium azide. Blood pressures were all taken in the sitting position — six times a day by nurses in the hospital and five times a day by the patient at home.

Four separate periods, varying from fourteen to thirty-seven days, are considered. The first is the initial hospital admission when antihypertensive therapy was instituted. The second is a representative fortnight of good control, when asymptomatic normotension was present. The third is a fortnight of lowered blood pressure despite diminished intake of medication after acute arthritis had appeared. The fourth is the second hospital admission, during which hydralazine was stopped and two ineffective agents substituted for it. During this admission the ganglionic blocking agent was switched from hexamethonium chloride to pentolinium tartrate and back again. (Table 2 lists the average systolic deviation for this patient.)

the pentolinium recovery was much higher, amounting to 36 per cent (Table 3).*

The second patient was a twenty-five-year-old laborer whose illness had begun three months before hospital entry with emesis followed by pedal edema and then dysuria. On admission the blood pressure was 264 systolic, 150 diastolic. There were hemorrhages, exudates and papilledema in the ocular fundi, and cardiomegaly and a gallop rhythm were present; anasarca was evident. Examination of the blood revealed a red-cell count of 3,650,000 and a white-cell count of 28,900. Urinalysis showed a ++++ test for albumin. The nonprotein nitrogen was 49 mg. per 100 cc. A muscle biopsy was positive for periarteritis nodosa. Symptomatic improvement followed the administration of 300 mg. of cortisone per day and 10 to 15 mg. of hexamethonium chloride parenterally every two hours, with an initial reduction of blood pressure to 160 systolic, 110 diastolic; however, within ten days hypertension (blood pressure of 200 systolic, 140 diastolic) was temporarily re-established and remained for the next ten days despite an increase in autonomic blocking agent to as much as 40 mg. of pentolinium tartrate intramuscularly every two hours. At this point increasing amounts of sodium azide were added. Table 3 gives the mean blood pressure and total antihypertensive drug therapy, as well as pentolinium recovery by days somewhat later during the period of change from parenteral to oral medication. The apparent recovery of parenterally administered pentolinium ion was over 99 per cent in the interval chosen, and that of orally administered drug was 22 per cent.† With the failure of sodium azide, hydralazine was substituted. At the time of discharge from the hospital after four months of therapy this man was weak but had no specific symptoms without cortisone. The blood pressure averaged 121 systolic, 67 diastolic, on 100 mg. of pentolinium tartrate and 100 mg. of hydralazine orally four times a day.

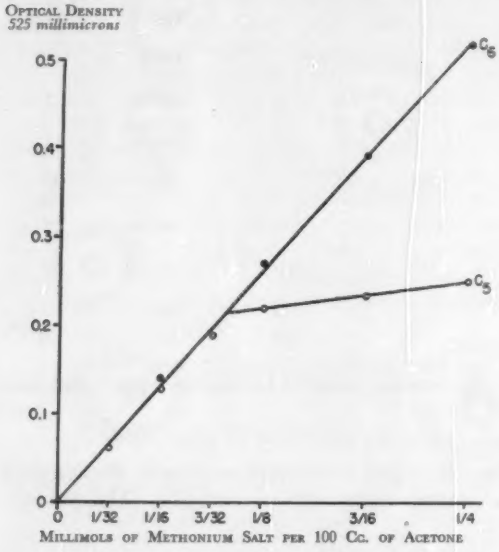

Figure 4. *Plot of 525-Millimicron Optical Density As a Function of Methonium Reineckate Concentration in Acetone.*

The open circles indicate the values for pentolinium, and the solid circles the values for hexamethonium ions. The two sets of data were simultaneously obtained by the addition of 20 cc. of fresh saturated ammonium reineckate to 100 cc. of known concentrations of each methonium salt, the water-insoluble methonium reineckate then being filtered, washed and redissolved in five successive 20-cc. portions of acetone, which were then pooled, and the optical density read at 525 millimicrons on the Beckman spectrophotometer. For low concentrations the curves are identical for the two methonium ions. The solubility of hexamethonium reineckate in acetone is sufficiently high that there is no practical chance of achieving saturation. The solubility of pentolinium reineckate, however, is markedly less, and care must be taken to avoid falsely low assay values as a result of leaving some undissolved on the filter. The slight slope of the final segment of the pentolinium curve is presumably due to incomplete saturation, although the possibility of more than one component in the solution cannot be excluded.

Discussion

As a chemical sympathectomizing agent pentolinium tartrate demonstrated a limited but definite improvement over other methonium salts for some, but not for all, patients. By weight it was approximately five times as effective in lowering elevated blood pressure as hexamethonium chloride; ion for ion it was ten times as powerful. Although every unpleasant manifestation of autonomic blockade has been observed, there usually was relatively less parasympatholysis and hence fewer and milder untoward reactions. It was most useful in persons with very severe hexamethonium side effects, particularly those who needed the greatest amounts of that drug for effective control of blood pressure. Unfortunately, the vasomotor instability accompanying normotension in occasional patients requiring large hexamethonium dosages was often more frequent and persistent with pentolinium tartrate.

Substituted hydrazines remain unique substances without which we have been unable to control the most severe stages of hypertension, even with enormous doses of blocking agents. A difficult therapeutic problem is the patient in whom acute arthritis or disseminated lupus erythematosus has developed after hydralazine.[14-16] Pentolinium salts are no more potent than other methonium compounds in preventing a recrudescence of hypertension in a recalcitrant form.

*The mean values cited in the text were obtained from the final line of Table 3. The eight values comprising this line are five-day totals obtained by addition of the enclosed figures in each column. The periods were chosen so as to be as comparable as possible without injecting any unnecessary uncertainty from possible overlapping. In the patient with severe benign hypertension the first four days of methonium therapy were not included because of rapidly changing conditions generated by the institution of treatment. The two days when both agents were given, pentolinium tartrate being substituted for hexamethonium chloride, are also omitted because of some uncertainty about how much of each agent was present in the urine.

†See footnote to previous case. The two five-day periods were chosen so as to be contiguous.

For a pair of such patients considered here, pentolinium ion combined with continued hydralazine resulted in improved blood-pressure control; however, the tendency to low blood pressure that accompanies collagen disease of this etiology in chemically sympathectomized patients[16] suggests that the process may not have completely regressed. On the average this pair required only a tenth as much pentolinium tartrate as hexamethonium chloride and a fourth as much hydralazine as previously. In sharp contrast the dozen patients without evidence of hydralazine toxicity needed a fifth as much pentolinium tartrate as hexamethonium chloride although their hydralazine intake remained unchanged. A further comparison revealed that the other 4 patients who manifested hydralazine toxicity and whose hydralazine was therefore discontinued failed to achieve their previous degree of blood-pressure control with a pentolinium dosage almost two fifths that of their prior hexamethonium intake.

About 5 per cent of ingested hexamethonium chloride is excreted unaltered by the kidneys.[13] In 2 patients the recovery of pentolinium tartrate was almost sixfold greater, being reminiscent of the curious observation that hexamethonium tartrate is better absorbed than the chloride in human beings.[19] Wien apparently found up to 20 per cent of orally administered pentolinium tartrate in the urine of animals.[5] The increased pentolinium absorption may be a factor in its high potency; however, the fivefold differential between the two agents injected parenterally[5] suggests that the urinary recoveries of orally administered pentolinium ion here reported may have been unusually high. Metabolism of methonium ions by liver may explain pharmacologic variations.[20]

TABLE 3. *Urinary Recovery of Pentolinium Ion in 2 Patients.*

DAY	PATIENT WITH SEVERE BENIGN HYPERTENSION						PATIENT WITH PERIARTERITIS NODOSA					
	MEAN BLOOD PRESSURE	HEXAMETHONIUM ION*	PENTOLINIUM ION*	HYDRALAZINE*	OUTPUT OF HEXAMETHONIUM	OUTPUT OF PENTOLINIUM	MEAN BLOOD PRESSURE	PENTOLINIUM ION†	PENTOLINIUM ION*	SODIUM AZIDE*	OUTPUT OF PENTOLINIUM†	OUTPUT OF PENTOLINIUM*
		mg./day	*mg./day*	*mg./day*	*mg./day*	*mg./day*		*mg./day*	*mg./day*	*mg./day*	*mg./day*	*mg./day*
1	206/134						157/114	121		0.84	10.3	
2	183/129	278			0.00		166/119	125		0.88	72.9	
3	196/116	834			1.03		175/124	130		1.22	95.9	
4	180/119	1,388			6.61		175/126	130		1.29	154.0	
5	176/116	1,850			59.0		174/133	129		1.62	112.0	
6	180/115	2,220		75	157.0		180/135	114		1.29	130.0	
7	183/125	2,220		225	306/2		185/133	167		1.94	166.0	
8	180/123	2,220		375	306/2		171/129	100		1.78	117.0	
9	175/109	2,220		500	108.0		171/126	138		1.62	121.0	
10	172/116	2,220		600	160.0		163/129		359	2.59		94.6
11	175/123	1,666	133	600	105.0		173/133		416	3.23		87.2
12	166/111	555	400	600	61.7‡	13.9‡	168/121		396	1.94		164/2
13	156/106		356	600		106.0	176/129		359	3.55		164/2
14	138/93		312	600		82.2	178/133		534	3.55		101.0
15	139/104		156	550		63.1						
16	133/85		133	625		76.3						
17	138/86		200	625		84.9						
Totals of enclosed values		11,100	1,157		731.0	413.0		648	2,064		646.0	447.0

*By mouth.
†By intramuscular injection.
‡Attempt to distinguish hexamethonium & pentolinium ions by their differential acetone solubility & hence by different rates of removal from filter.

SUMMARY

Twenty-four patients in severe "benign" and malignant stages of hypertension were treated with pentolinium tartrate and hydralazine. When begun before the appearance of frank uremia, the combination gave satisfactory control of the worst cases of hypertension. Although quantitatively more potent in its effect on blood pressure, pentolinium tartrate was qualitatively similar to other methonium compounds. Sometimes it produced marked variations in systolic pressure. Six patients in whom collagen disease had followed the administration of hydralazine were given pentolinium tartrate combined with other drugs, with varying results.

We are indebted to Betty F. Perry for the extensive mathematical calculations involved.

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A STUDY OF ILLNESS IN A GROUP OF CLEVELAND FAMILIES*

VIII. Relation of Tonsillectomy to Incidence of Common Respiratory Diseases in Children

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THE question of whether or not an excessively large number of common respiratory infections, chiefly "common colds," in a child constitutes an indication for tonsillectomy continues to receive a variety of answers.[1-5] Most recent lists of indications, however, do not include the frequent occurrence of common respiratory diseases per se as a major or primary indication for this operation.[2,3] The closely related question of whether or not a reduction in the incidence of common upper respiratory infections may be expected after tonsillectomy has been given considerable attention. The answer has been sought in several ways, including follow-up studies of patients operated on,[6,7] studies comparing the occurrence of respiratory infections among children who had and who had not had their tonsils removed[8,9] and parents' evaluation of the benefit of the operation.[10]

There are apparent contradictions in the evidence obtained from these various sources. These may be due to a variety of factors. For instance, the fact that the rate of occurrence of the common respiratory diseases decreases with age[11-13] has not always been taken into consideration; a decrease in number of respiratory infections might be expected when children are observed over a period of time regardless of whether or not they have a tonsillectomy. In addition, when memory is relied upon to provide information concerning a child's health status over a period of years, inaccuracies are certain to occur. These and other problems in evaluating the benefits of tonsillectomy are discussed by Illingworth.[14]

The present paper is one of a series that considers factors related to the occurrence of the common respiratory diseases. Because careful records have been kept for each person in a group of families over a period of several years, it has been possible to determine accurately the incidence of the common respiratory diseases and to compare the incidence of these infections among children whose tonsils had been removed with that among those whose tonsils were intact.

Materials and Methods

This study is based on observations made of a group of Cleveland families during the period 1948-1952. A detailed account of the methods used, as well as a general description of the population, has been presented previously.[15] During the period reported here approximately 230 children were under observation for varying lengths of time. Daily records of the health status of each person were kept by the mothers. The families were visited weekly by field workers,

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This investigation was conducted under the sponsorship of the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, and was supported in part by the Office of the Surgeon General, Department of the Army, and by grants from the Brush Foundation, the Cleveland Foundation, the S. P. Fenn Trust, Mr. Philip R. Mather and the Republic Steel Corporation.

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and at the time of illness the patient was examined by a staff physician, who evaluated the illness and obtained throat cultures and other specimens as indicated. The mothers' records, together with observations by the field workers and physicians, provided the data for this study.

The illnesses included in this report are those previously described as the common respiratory diseases.[15] This group includes those illnesses in which symptoms referable to the respiratory tract occurred, after exclusion of specific entities such as the common childhood diseases, streptococcal infections, nonstreptococcal exudative tonsillitis and pharyngitis, the viral and bacterial pneumonias, influenza diagnosed by virus isolation and illnesses considered to be allergic.

Two sorts of data are presented. In the first place, the occurrence of the common respiratory diseases among all children of the family population three years of age and older is considered separately for those whose tonsils had been removed and for those whose tonsils were intact; no child under three years of age had had a tonsillectomy. Secondly, the occurrence of these illnesses among 26 children who had a tonsillectomy while under study is shown, both for the period of observation before and for the period after operation. Each child did not have the same length of observation before as after tonsillectomy; therefore the preoperative and postoperative data are not balanced for individual children. Such data, however, make it possible to examine the average incidence of common respiratory diseases in the same group of children before and after tonsillectomy.

TABLE 1. *Age-Specific Rates for Common Respiratory Disease According to Presence or Absence of Tonsils (Total Experience, 1948-52).*

AGE	CHILDREN WHO HAD HAD TONSILLECTOMY			CHILDREN WHO HAD NOT HAD TONSILLECTOMY		
	PERSON-DAYS	NO. OF CASES OF COMMON RESPIRATORY DISEASE	CASES PER 1000 PERSON-DAYS	PERSON-DAYS	NO. OF CASES OF COMMON RESPIRATORY DISEASE	CASES PER 1000 PERSON-DAYS
3-5	9,675	212	21.9	75,085	1,669	22.2
6-7	16,105	307	19.1	28,777	505	17.5
8-9	16,851	282	16.7	12,089	177	14.6
10+	19,076	288	15.1	5,561	105	18.9

All results are expressed as incidence rates of common respiratory diseases among children who had had a tonsillectomy and among those who had not. Comparisons of these data require the use of either age-specific or age-adjusted rates because the incidence of common respiratory illnesses changes with age and the post-tonsillectomy experience is heavily weighted with older children. When comparison is made between the preoperative and postoperative rates of the children who underwent tonsillectomy during observation in this study, an additional adjustment for season is necessary because 10 of the 26 tonsillectomies were performed during May and June. Since the rates for the common respiratory diseases are fairly constant between September and April and lower between May and August[15] the seasonal adjustment was based on these two groups of months. No adjustment was made for calendar year because of the constancy of the rates from one year to the next.[15] Adjustment for age and season was performed according to method A of Pearl.[16]

TABLE 2. *Age-Adjusted Rates for Common Respiratory Disease among Children Three Years of Age or Older by Diagnosis and According to Presence or Absence of Tonsils (Total Experience, 1948-52).*

DIAGNOSIS*	ILLNESSES PER 1000 PERSON-DAYS	
	CHILDREN WHO HAD HAD TONSILLECTOMY	CHILDREN WHO HAD NOT HAD TONSILLECTOMY
Questionable respiratory diseases	2.5	2.4
Coryzal illnesses	14.0	13.7
Acute respiratory diseases	2.1	1.9
Other illnesses	1.1	1.2
Totals	19.7	19.2

**Questionable respiratory diseases:* illnesses so mild that decision difficult whether true infection present.

Coryzal illnesses: those that might be thought of as common colds or severe common colds.

Acute respiratory diseases: those, frequently febrile, with prominent symptoms referable to throat & lower respiratory tract.

Other illnesses: include, principally, influenzalike and more obscure respiratory illnesses.

The incidence rates among the 26 children who had their tonsils removed while under study are subdivided according to number of years before and after tonsillectomy. The years referred to are not calendar years, but begin on September 1 and end on the following August 31; these time units were chosen because they correspond roughly to the respiratory-disease cycle. Thus, for a child who had a tonsillectomy on April 1, 1950, the experience between September 1, 1949, and August 31, 1950, would be classed as "year of tonsillectomy"; his experience between September 1, 1948, and August 31, 1949, would be considered as "first year before tonsillectomy" and so forth. The year of tonsillectomy is further divided into the time before and the time after operation so that, for the hypothetical person whose tonsillectomy was performed on April 1, 1950, the period from September 1, 1949, through March 31, 1950, is included as "year of tonsillectomy, before operation" and the period April 1 through August 31, 1950, as "year of tonsillectomy, after operation."

RESULTS

Tables 1 and 2 are based on the observations made during the period 1948-1952 of all children who were three years of age or over. Rates are presented separately for children who had had their tonsils removed and for those whose tonsils were present. When considered on an age-specific basis (Table 1) the rates

for the two groups were quite similar, showing no consistency in the direction of the slight differences that existed. Total age-adjusted rates (Table 2) for the two groups were almost identical: 19.7 common respiratory illnesses per 1000 person-days for those children who had undergone tonsillectomy, and 19.2 for those who had not been subjected to this operation.

The age-adjusted rates for each of several diagnostic classes of the common respiratory diseases (Table 2) reveal differences between the two groups of children that were slight and reflected only the minor difference in the total age-adjusted rates.

TABLE 3. *Observed and Expected Attack Rates of Common Respiratory Diseases According to Time before and after Tonsillectomy.*

PERIOD BEFORE OR AFTER TONSILLECTOMY	PERSON-DAYS	NO. OF CASES EXPECTED*	NO. OF CASES OBSERVED	RATES PER 1000 PERSON-DAYS	
				EXPECTED*	OBSERVED
Before operation:					
3d yr. or earlier	2725	55	65	20.2	23.9
2d yr.	4546	104	114	22.9	25.1
1st yr.	7716	166	180	21.5	23.3
Yr. of tonsillectomy	5310	119	145	22.4	27.3
After operation:					
Yr. of tonsillectomy	4063	66	74	16.2	18.2
1st yr.	7886	163	166	20.7	21.0
2d yr.	5607	105	126	18.7	22.5
3d yr. or later	3383	63	58	18.6	17.1

*Expected numbers based on age-specific & season-specific rates for entire population.

Table 3 refers to the 26 children whose tonsils were removed while they were under observation in this study. These children were five to nine years of age at the time of tonsillectomy. The expected numbers in this table are the number of cases that would be expected in this group of 26 children on the basis of the age-specific and season-specific rates of the entire family population. A comparison of the observed and expected rates shows that tonsillectomy did not materially alter the average incidence of common respiratory disease. The average rate among these 26 children had been higher than that expected for several years before tonsillectomy and continued to be higher than expected after the operation.

DISCUSSION

This report presents the occurrence and severity of common respiratory diseases among a group of children who had had their tonsils removed and a group who had not. Neither the complications of respiratory diseases nor the frequency of streptococcal illnesses among the two groups of children has been investigated.

Attack rates from the common respiratory diseases in the present study were no lower among children who had had their tonsils removed than among those who had not had this operation. This finding is consistent with the studies reported by the Medical Research Council[8] and by Paton,[9] both of which were conducted among older children in boarding schools and were based on records of illnesses resulting in absence from classes. These two studies, as well as the present one, are free from the inaccuracies inherent in those that rely on memory.

The diagnostic subgroups employed here (Table 2) provide an index of the severity of illness based on the prominence and duration of certain symptoms. The attack rates of each of these various types of upper respiratory disease were almost identical for the two groups of children. This is in agreement with the findings of the Medical Research Council, which used a similar system of classification. Paton[9] found that colds and bronchitis occurred somewhat more frequently in those whose tonsils had been removed, whereas tonsillitis occurred less frequently and pharyngitis with about the same frequency as in those who had not had tonsillectomy. Mertz,[17] using another index of severity, found the incidence of disabling respiratory illnesses (those causing interruption in daily activities) and the duration of disability to be very similar among children who had had tonsillectomy and those who had not.

The fact that the attack rates of the common respiratory diseases were no lower among children who had had tonsillectomy than among children who had not had this operation is not, in itself, evidence that the operation was of no value in reducing the incidence of these infections. Without knowledge of the attack rates before operation, it is impossible to determine whether or not illness rates were changed after tonsillectomy.

The data for the 26 children who underwent tonsillectomy while in this study do, however, provide direct evidence that the operation did not influence the incidence of common respiratory disease. These children, on the average, had an excessively high rate before and continued to have an excessively high rate after operation. This is at variance with the results reported by the Medical Research Council.[8] The 364 boys who underwent tonsillectomy while under observation in that study had, on the average, more than the expected number of nasopharyngeal infections before tonsillectomy but fewer than expected after operation. There are certain notable differences, however, between the Medical Research Council study and the present one. The age distribution of the boys observed both before and after tonsillectomy in the former study is not given, but it is unlikely that any were under seven years of age at the time of operation; on the other hand, 21 of the 26 children reported upon here were under seven at the time of operation. The nasopharyngeal infections reported in the Medical Research Council study included only

illnesses requiring absence from classes for a day or more, whereas in the present study any symptom abnormal for the child concerned was considered sufficient to designate the presence of an illness. The former study did not exclude streptococcal and nonstreptococcal exudative tonsillitis and pharyngitis, whereas these were excluded from the common respiratory diseases considered here. Although the seasonal distribution of the period of observation before and after tonsillectomy in the Medical Research Council study was not stated, it is possible that seasons characterized by a high incidence of common respiratory disease were not equally divided between preoperative and postoperative periods. This factor was found to be important in the present study in evaluating the rate of illness immediately after tonsillectomy and has been taken into account here by the use of rates adjusted for age and season. Which, if any, of these factors were responsible for the lack of agreement between the findings of these two studies is not known.

In a somewhat different type of investigation, Kaiser[6,7] conducted parallel follow-up examinations on two groups of children of comparable ages. Both were reported to have had the same indications for tonsillectomy, but, for various reasons, the operation was performed only on the children in one group. These children were examined and questioned about illnesses one, three, and ten years after tonsillectomy had been performed. At the same time the group of children who had not had this operation were examined and questioned. The data presented are difficult to interpret. Kaiser,[7] referring to common colds, otitis media, sinusitis and laryngitis, concluded, "it cannot be demonstrated that the tonsils are often a causative factor in these infections; consequently tonsillectomy does not offer a solution for their eradications save in exceptional cases." The findings of the present study are consistent with this conclusion.

Summary

The relation between tonsillectomy and incidence of common respiratory diseases as part of a broad study of illness in a group of families has been investigated.

Attack rates for the common respiratory diseases among children who had had a tonsillectomy were very similar to those among children of comparable age who had not had this operation. There was no indication of a difference in type of common respiratory disease between the two groups of children.

The 26 children who had a tonsillectomy while under observation were found to have had a higher than expected rate of common respiratory disease both before and after operation. Tonsillectomy did not materially alter this incidence.

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Correction. In the second sentence of the second paragraph under the heading "Indications for Therapeutic Abortion," on page 512 of the article "Management of the Pregnant Patient with Cardiac Disease," by Dr. William Horowitz, which appeared in the March 31 issue of the *Journal*, the word "hysterectomy" should be changed to "hysterotomy."

ESTIMATION OF URINARY REDUCING CORTICOSTEROIDS WITH BLUE TETRAZOLIUM*

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DETERMINATION of the concentration of the corticosteroids in urine has become an increasingly important problem. A variety of methods have been proposed for their estimation, based on the reducing properties of the alpha-ketol side chain at C_{17}, on the formaldehydogenic potential of this side chain or on empiric, poorly understood color reactions of this molecular species.

The most reliable method is that of Talbot and his associates,[1] which, although complicated and therefore impractical for general use, has the distinct advantage of nearly proving the main structural features of the corticosteroids in each determination. The steps of the procedure demonstrate in turn that the material is lipid, neutral, ketonic, partitions between water and benzene like the corticosteroids and unlike other steroids, and has a reducing group in the side chain. Although losses are inevitable with a procedure utilizing so many reactions and steps, all shorter and simpler methods must rely for their justification on the results with this more elaborate method.

After the synthesis of a ditetrazolium chloride that yields a blue diformazan on reduction[2] and the development, therewith, of colorimetric methods for a variety of dehydrogenating enzymes,[2] as well as a histochemical method for succinic dehydrogenase,[3-6] it was shown that this ditetrazolium salt was reducible at elevated pH with a variety of substances possessing an enol, alpha-aldol, alpha-ketol[3] or sulfhydryl group.[3,7] It occurred to us, as well as to others,[8-10] that blue tetrazolium could serve as a basis for demonstrating the reducing properties of the alpha-ketol side chain of the corticosteroids in estimating their concentration in urine. It was expected that water-soluble reducing agents such as ascorbic acid and glucose could easily be separated from the lipid soluble corticosteroids. Published procedures utilizing blue tetrazolium, however, are not sensitive enough for the assay of urine.[9] One such method was developed for assaying the high cortisone content of pharmaceutical preparations.[10] We observed that with those procedures the color density was not strictly proportional to the amount of corticosteroid (at low concentration) because the reaction was not going to completion. When the amount of hot alkali was increased from 0.033 to 1.02 N (a thirty-one-fold increase) reduction was complete, and the sensitivity of the test for corticosteroid was increased eight-fold. With the increased reaction rate and sensitivity afforded by hot, strong alkali, the ordinary solvents, which had been used previously, gave high blank values that were due to decomposition of the solvent or impurities in it. After an extensive search for an ideal solvent, which in addition to giving low blanks with the reagents should be polar, dissolve corticosteroids in high concentration, be miscible with water and boil above 100°C., the best proved to be diethylene glycol dimethyl ether, purified by vacuum distillation from lithium aluminum hydride.

The present paper gives the detailed procedure for estimating total corticosteroids (free as well as glucuronic acid conjugate) in the urine after enzymatic hydrolysis with β-D-glucuronidase, evidence for the specificity and reliability of the method, preliminary results of assay of normal and abnormal urine and a brief discussion of the results as compared with other methods.

METHOD

Reagents

Reagents used are as follows:

1N sodium hydroxide.

1N hydrochloric acid.

0.2 N acetic acid-sodium acetate buffer, pH 4.8.

Concentrated hydrochloric acid.

Commercial β-D-glucuronidase.**

Anhydrous sodium sulfate.

Dichloromethane (methylene chloride).

0.1 N sodium hydroxide.

0.01 N sulfuric acid.

*From the Yamins Laboratory for Surgical Research and Endocrine Laboratory, Beth Israel Hospital, and the departments of Surgery and Medicine, Harvard Medical School.

Supported by a research grant (C312-C8) from the National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare, by the Slosberg Fund for Research in Diabetes and by an institutional grant to Harvard University from the American Cancer Society.

Acknowledgment for technical assistance at various stages in the development of the method is due Rhoda Lewis, Virginia Rosenberg, Barbara Rothbell, Robert Eisendrath, Miriam Winer, Earl Whipple and Norman Diamond.

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**Glucuronidase of liver origin was purchased from Tec Chemical Corporation, Stamford, Connecticut, and from Warner Chilcott Corporation, New York City, that of splenic origin from General Biochemical Corporation, 677 Laboratory Park, Chagrin Falls, Ohio, and that of bacterial origin from Sigma Corporation, St. Louis, Missouri. Enzyme powder was more satisfactory than the available aqueous preparations, which contained a troublesome emulsifying agent. The optimum amount of glucuronidase was determined with every new batch purchased. The best material was assayed at 50,000 Fishman units per gram.

Diethylene glycol dimethyl ether,* distilled† from lithium aluminum hydride.
Blue tetrazolium† (a solution of 37.5 mg. in 100 cc. of distilled water may be stored at 4°C. for at least two months).
2.25 N sodium hydroxide.
2.25 N acetic acid.
Anhydrous ethyl acetate.

Procedure

Enzymatic Hydrolysis of Steroidal Glucuronides

To determine total corticosteroid (free as well as glucuronic acid conjugate) it was necessary to hydrolyze the conjugated steroids. A 50-cc. aliquot of a twenty-four-hour output of urine was brought to pH 6.0-6.5‡ with either sodium hydroxide (1 N) or hydrochloric acid§ (1 N). The urine was boiled under reflux for ten minutes to destroy glucuronidase inhibitors and cooled to room temperature. Five¶ cubic centimeters of acetic acid in sodium acetate buffer (0.2 N, pH 4.8) was added. The pH was adjusted to 4.8 with hydrochloric acid (1 N). β-D-glucuronidase (150 mg., or 7500 Fishman units) was added, and the solution was incubated overnight at 50 to 55°C. in a glass-stoppered bottle.

Extraction of Steroid

The urine was cooled to room temperature and acidified with concentrated hydrochloric acid to pH 1.0, saturated with anhydrous sodium sulfate and extracted with three portions of dichloromethane (30 cc.) by shaking of each for three minutes in a 100-cc., glass-stoppered Pyrex reagent bottle held by the neck to avoid evaporation of the solvent (boiling point 40°C.). Shaking was also accomplished mechanically with a multiple-holder, wrist-action shaker.‖ The stopper was secured with a heavy rubber band along the vertical axis of the bottle to prevent seepage. It was usually necessary to break emulsions** by centrifugation for five to fifteen minutes at 1500 revolutions per minute with the bottle in a trunion cup. Sometimes, the emulsion broke when the bottle was placed in ice water for a few minutes; such cooling was usually more successful after the second and third extractions. The two phases were separated first by gentle decanting of as much of the supernatant urine as possible. The rest was gently poured, so as to avoid emulsification, into a separatory funnel. Because of the potent solvent action of dichloromethane on stopcock grease, silicone-high vacuum grease was applied to the stopcock, which was wedged in tightly, and the precaution was taken to place another Pyrex reagent bottle directly beneath the funnel until the solvent was ready to be separated. The urine phase was returned to the original Pyrex bottle, more solvent was added, and the process was repeated as mentioned above. The combined dichloromethane extracts were washed by shaking for three minutes in a Pyrex bottle successively with 18 cc. of chilled 0.1 N sodium hydroxide and 18 cc. of chilled 0.01 N sulfuric acid. The extracts were stored in a refrigerator to prevent loss by evaporation. Under these conditions loss of solvent for the whole procedure was rarely more than 5 cc. to 10 cc. owing to evaporation and solution and suspension in water. For greater accuracy a partial restoration to 90 cc. of solvent lost by evaporation and solution could be made, but we have not attempted to make such estimations. The dichloromethane extract was dried by shaking in a glass-stoppered reagent bottle†† with 2 gm. of anhydrous sodium sulfate for a few minutes. Occasionally, more sodium sulfate was required to clarify the solvent. It was decanted into another bottle. Duplicate aliquots of the 90 cc. of dichloromethane used were taken. A convenient way of keeping the final optical density in the proper range‡‡ was to take a volume of solvent in cubic centimeters equal to the ratio of total urine volume divided by 140. These aliquots were placed in rimless test tubes (150 by 16 mm.) in a water bath at 50°C. and evaporated by a jet of filtered air until nearly dry. The last traces of solvent were then removed by water-pump suction (pressure of 40 mm. of mercury) applied through a one-hole rubber stopper for fifteen minutes while the tubes were immersed in a water bath at 50°C. The unused extract was stored in the cold so that repeat determinations could be made with larger or smaller aliquots for abnormal urine.

Colorimetric Assay

The steps of the color reaction are as follows:
Add 0.2 cc. of diethylene glycol dimethyl ether to each test tube of dry urinary extract and dissolve by agitation. Control tubes contained

*Purchased from Ansul Chemical Company, Marinette, Wisconsin. The commercial preparation is actually a mixture of ethers and may vary in composition. Whether interfering substances are present can only be determined after purification with lithium aluminum hydride.

†Blue tetrazolium, or 3,3 dianisole bis-4,4′ (3,5 diphenyl) tetrazolium chloride, and purified diethylene glycol dimethyl ether are both obtainable from Dajac Laboratories, Division of Borden Chemical Company, 511 Lancaster Street, Leominster, Massachusetts. We recommend that those inexperienced in vacuum distillation purchase purified diethylene glycol dimethyl ether because of the reported danger of explosion in the purification of methyl ethers with lithium aluminum hydride.[11] Since the calibration curves vary a little with the composition of the solvent, such a curve should be prepared with each new batch of solvent purchased.

‡This and all other pH changes referred to were made with a glass electrode.

§Preliminary adjustment of highly alkaline urine to a pH near 7.0 was accomplished by the dropwise addition of concentrated hydrochloric acid to avoid significant increase in volume.

¶Ten cubic centimeters of buffer is required if the twenty-four-hour output of urine is in excess of 2000 cc.

‖Manufactured by Burrell Corporation, Pittsburgh, Pennsylvania.

**The higher the urinary protein content, the greater the emulsification and consequent underestimation of urinary corticosteroid from loss at the emulsion interface.

††Up to this point in the procedure the glassware was adequately cleaned with detergents. All glassware beyond this point was cleaned with chromic sulfuric acid, to remove reducing agents, and rinsed thoroughly with distilled water.

‡‡The relation of optical density to volume of urinary extracts approached linearity when colorimetric readings were in the range equivalent to that of 10 to 25 microgm. of cortisone. When the colorimetric readings were less the color density did not always bear a linear relation to concentration of reducing substances in the extract. Therefore, when the colorimetric reading of the urine extract was less than that equivalent to 10 microgm. of cortisone, a larger aliquot of methylene chloride extract was re-evaporated for reassay, preferably at the approximate equivalent of the standard (20 microgm. of cortisone).

only the glycol and the glycol and 20 microgm. of cortisone (free alcohol).

Add 1 cc. of solution of blue tetrazolium (0.037 per cent).

Add 1 cc. of 2.25 N sodium hydroxide.

Agitate tubes to mix (do not use stoppers, tinfoil or parafilm covers).

Place tubes for fifteen minutes in a glycerol bath at 100°C.

Cool tubes in ice water.

Add 1 cc. of 2.25 N acetic acid.

Add 10 cc. of anhydrous ethyl acetate and shake thoroughly (rubber stopper may be used).

Centrifuge at 2500 revolutions per minute for one minute to clarify.

Decant ethyl acetate layer into a colorimetric tube and measure color density through a 560-millimicron filter with a colorimeter (Klett).

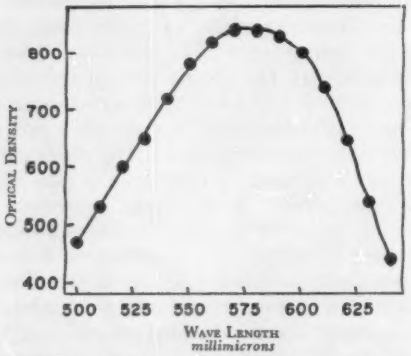

FIGURE 1. *Visible Absorption Spectrum of the Reaction Product Obtained upon Heating of 12.5 Microgm. of Cortisone with Blue Tetrazolium in Alkaline Solution.*

The diformazan was extracted into ethyl acetate for measurement with a Coleman Junior Spectrophotometer. (Compare with the absorption spectrum obtained in chloroform.[5])

The reason for selecting the 560-millimicron filter is shown in the spectrophotometric absorption curve of the diformazan in ethyl acetate (Fig. 1). Results with 540 and 580 filters were not as satisfactory.

Preparation of Calibration Curve

A calibration curve was prepared by the substitution of cortisone* (free alcohol) for the urinary extract in the colorimetric assay at increments of 5 microgm. over the range of 0 to 25 microgm. A linear relation to optical density was obtained over this range (Fig. 2). At higher concentration a marked departure from linearity was observed. Therefore, extrapolation from such a calibration curve could be made in the range of 25 to 35 microgm., or a smaller aliquot of the dichloromethane extract could be taken. In the linear portion of the curve each microgram of cortisone was equivalent to about 22 to 25 divisions of the Klett colorimeter. The reproducibility of the colorimetric portion of the assay (excluding hydrolysis and extraction) was ± 1.1 per cent. The diethylene glycol dimethyl ether was tested separately for purity with the reagents. With proper purification, optical-density readings (Klett) were under 10 divisions. Other batches, even after purification with lithium aluminum hydride, could not be made to give blanks less than 25 divisions of the Klett. It is essential, therefore, for each investigator to determine the purity of the solvent that he purchases and to provide his own calibration curve. This is especially important since batches of the solvent that gave blanks of 40 divisions or over gave calibration curves that were not linear below 10 microgm. of cortisone, although the curves were still linear from 10 to 25 microgm.

*Provided through the courtesy of Dr. Elmer Alpert, Merck and Company, Rahway, New Jersey, Dr. Emanual B. Hershberg, Schering Corporation, Bloomfield, New Jersey, and Dr. Roy Gencarelli, Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey.

Calculation

The number of milligrams of corticosteroids in a twenty-four-hour sample of urine was calculated in equivalents of cortisone from the following equation:

$$\text{mg. per 24 hr.} = \frac{\text{unknown O.D.}}{\text{standard O.D.}} \times \frac{\text{micrograms of standard}}{1000} \times \frac{90}{\text{cc. of extract evaporated}} \times \frac{\text{cc. of urine (24 hr.)}}{50}$$

Results

Table 1 shows our findings in presumably normal patients and hospital personnel. The values ranged from 4.1 to 7.5 mg. of urinary total corticosteroids per twenty-four hours. These results are in fair agreement with the values of 2.0 to 7.4 mg. of tetrahydrocortisone per twenty-four hours found by Baggett, Kinsella and Doisey[12] measuring the elutriate from paper chromatography with the Porter and Silber[13] reaction. The total urinary corticosteroids would be expected to be somewhat higher than the values obtained for tetrahydrocortisone.

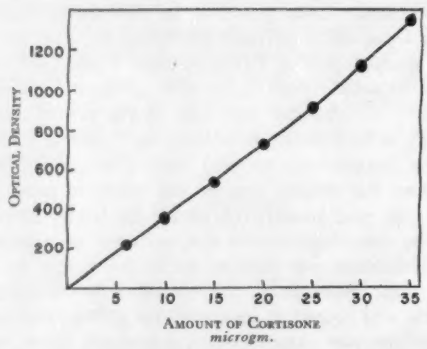

FIGURE 2. *Demonstration of the Linear Relation between Optical Density and Concentration of Cortisone (0 to 25 Microgm.) in the Colorimetric Assay.*

Optical densities are given as Klett-colorimeter readings multiplied by 2.

Patients with primary or secondary (myxedema) hypoadrenalism excreted between 1.2 and 2.4 mg. of

total corticosteroids per twenty-four hours (Table 2). In hyperadrenalism due to Cushing's syndrome or a virilizing adrenal carcinoma values of 12.4 and 14.3 mg. of urinary total corticosteroids per twenty-four hours were obtained (Table 2).

Striking increases in the excretion of total corticosteroids over previous levels were observed in patients who were given ACTH or cortisone (Table 3).

Discussion

In the era when Talbot and his associates[1] developed their method for the assay of corticosteroids its application to chloroform or chloroform-ether urinary extracts resulted in measurement chiefly of corticosteroid present in the free state. Simpler technics were proposed soon thereafter by Heard and Sobel[14] and Heard, Sobel and Venning,[15] who measured the free neutral lipid fraction of urine with the oxidizing agent, phosphomolybdic acid. This reaction was not specific for the alpha-ketol group of the side chain at C_{17} because other ketosteroids were able to reduce phosphomolybdic acid, although less rapidly and in some cases less extensively. Therefore, even though the latter method could be employed to observe the changes in corticosteroid concentration of urine in a patient from time to time, it was not reliable as a means of measuring the absolute content of urinary corticosteroid. Another method, which was designed as a simple means of demonstrating urinary corticosteroids, involved conversion of the C_{21}-alcohol group of the alpha-ketol side chain to formaldehyde with periodic acid.[16] The formaldehyde was made measurable with chromotropic acid[17-19] by MacFayden's[20] procedure. Porter and Silber[13] recommended a color reaction for corticosteroids or their conjugates, which produced a yellow color when they were heated with phenylhydrazine and concentrated sulfuric acid.

In recent years these various methods have been applied to the measurement of urinary total corti-

Table 1. *Total Corticosteroids in Urine Collected for Twenty-Four Hours from 38 Normal Adults.**

	Amount Collected from Male Subjects	Amount Collected from Female Subjects
	mg.	*mg.*
	4.7	5.5
	4.5	5.4
	5.9	5.4
	5.7	4.3
	4.3	5.5
	4.9	5.7
	4.6	4.8
	4.8	5.4
	6.0	4.6
	5.0	6.4
	5.4	5.7
	5.8	4.5
	4.8	6.8
	7.5	4.4
	4.8	4.5
	6.6	7.0
	5.1	
	5.7	
	6.4	
	5.2	
	6.5	
	4.1	
Range	4.1-7.5	4.3-7.0
Mean	5.4	5.4

*Specimens collected from hospital patients & hospital personnel without endocrine disease or stress.

Table 2. *Total Corticosteroids in the Urine of Patients with Hypoadrenalism and Hyperadrenalism.*

	Diagnosis	Corticosteroids Excreted
		mg. per 24 hr.
Patients with hypoadrenalism:		
	Addison's disease*	1.4
	Addison's disease*	2.0
	Hypopituitary dwarfism	1.6 1.2
	Hypopituitarism* (Sheehan's disease)	2.4
	Dwarfism* & ovarian agenesis with ++ follicle-stimulating hormone	1.5
	Myxedema*	1.2
Patients with hyperadrenalism:		
	Virilizing adrenal carcinoma (proved by surgery)*	14.3
	Cushing's syndrome†	12.4

*We are indebted to Dr. Lewis Hurxthal, Lahey Clinic, for permission to study urines of these patients & for clinical diagnoses.

†We are indebted to Dr. Sidney Ingbar, Boston City Hospital, for permission to study this patient & for clinical diagnosis.

Table 3. *Effect of Administration of ACTH or Cortisone on Total Corticosteroid Excretion.*

Diagnosis	Excretion before Treatment	Excretion During Administration of ACTH or Cortisone
	mg. per 24 hr.	*mg. per 24 hr.*
Patients given ACTH:		
Cushing's syndrome*	12.4	18.3
Craniopharyngioma†	3.9	19.6
Patients given cortisone:		
Addison's disease†	2.0	12.1
Virilizing adrenal carcinoma (proved by surgery)†	14.3	31.1
Shock, prostatism, diarrhea	15.2‡	39.0‡

*We are indebted to Dr. Sidney Ingbar, Boston City Hospital, for permission to study this patient & for clinical diagnosis.

†We are indebted to Dr. Lewis Hurxthal, Lahey Clinic, for permission to study urines of these patients & for clinical diagnoses.

‡Partial collection of 24-hr. specimen.

costeroids obtained after prior hydrolysis with acid or the enzyme, β-glucuronidase. Utilizing the Porter and Silber[13] reaction, Reddy, Jenkins and Thorn[21] estimated the total urinary corticosteroids after extraction of the free and conjugates from urine with butyl alcohol. Although this method may be carried out simply and rapidly, it lacks specificity and sensitivity because of high urinary blank values.[21] The color reaction with phenylhydrazine in concentrated sulfuric acid has never been formulated and is given by other steroids[13] and other substances. Marks and Leftin[22] found that administration of potassium iodide, chloral hydrate or paraldehyde produced similar color changes to that of cortisone with the Porter and Silber[13] reaction as employed by Reddy, Jenkins and Thorn.[21] They also demonstrated that potassium iodide and iodine, when reacted in vitro with the Porter and Silber reagent, produced spectral absorption similar to that of the corticoids. It was found that some steroids gave even more color with concentrated sulfuric acid alone than with phenylhydrazine and sulfuric acid.[13] These facts indicate how poorly understood this interesting color reaction is. Nevertheless, the usefulness of the method for showing absolute changes in total urinary corticosteroid "as the index of choice in the routine measurement of adrenal cortical function" has been well demonstrated.[21]

TABLE 4. *Effect of Reducing Corticosteroids on Blue Tetrazolium in Hot Alkali.**

STEROID	FUNCTIONAL GROUP IN C_{11} POSITION	CORTISONE EQUIVALENT	OPTICAL DENSITY (KLETT)
		microgm.	
Cortisone	keto	24	416
Dehydrocorticosterone	keto	24	413
Hydrocortisone	hydroxy	24	214
Corticosterone	hydroxy	24	220
Desoxycorticosterone	hydrogen	24	197

*These results suggest that oxidation of the alpha-ketol side chain in corticosteroids with 11-hydroxyl group is only half as extensive as that in those with 11-keto group. Presumably, 11-hydroxyl group complexes with keto aldehyde formed on loss of 2 hydrogen atoms & prevents further oxidation under these conditions to keto acid. Presence or absence of 17-hydroxyl group apparently does not influence reaction. We have no explanation for low value obtained with desoxycorticosterone.

The present method for measuring total urinary corticosteroid, which consists mainly of tetrahydrocortisone,[12] has the advantages of equal simplicity and greater sensitivity and specificity for the corticosteroids with the alpha-ketol side chain.

The various steroids* that failed to react with blue tetrazolium under the present condition were as follows: one of the nor-cholestenols, allo-pregnanedione-3,20, dehydroisoandrosterone, cholesterol, androstane-3,17 dione, cholestanone, estrone, Δ^5 pregnenol-3, one-20, pregnanedione, 3-hydroxy-11-keto-etio cholanic acid methyl ester, and estradiol. Only the corticosteroids with an alpha-ketol in the side chain reacted. The corticosteroids with a hydroxyl group at C_{11} reacted only half as extensively as those with a keto group at C_{11} (Table 4). It is postulated that the C_{11} hydroxyl group complexes with the keto aldehyde to prevent further oxidation to the keto acid.† We have no explanation for the low value obtained with desoxycorticosterone.

*We are indebted to Professor Louis F. Fieser, of Harvard University, for samples of these steroids.

SUMMARY AND CONCLUSIONS

A new method for assaying the corticosteroids of urine with the reagent, blue tetrazolium, is described. The method is sensitive enough to enable the use of 50 cc. of urine; it is simple to execute, and it is specific for the reducing properties of the alpha-ketol group of the corticosteroids. The method measures total corticosteroids consisting of both the free and glucuronic acid conjugate. What little steroid is conjugated to sulfuric acid is not determined by this procedure.

The range in normal males and females is given, and the results with urine from patients with abnormal endocrine states are also presented. The results correlate with the clinical state. Increase in urinary corticosteroids after injection of ACTH or cortisone is demonstrated.

Various physiologic and pathologic conditions may act as a stress that will elevate the urinary corticosteroids excretion. Careful clinical evaluation is necessary before elevations in excretion are attributed to endocrinopathy.

†Our method was used by Dr. Nathan Talbot, Massachusetts General Hospital, to measure corticosteroids purified from urine by countercurrent distribution. He obtained good correlation with another method based on the reactivity of the 3-keto group. He also ran into the phenomenon of the lesser reactivity of corticosteroids with an 11-hydroxyl group as compared to an 11-keto group.

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INTRAUTERINE DEATH OF THE FETUS DUE TO ACCIDENTAL CARBON MONOXIDE POISONING*

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ALTHOUGH carbon monoxide poisoning in pregnant women was reported in 1859, very little has been written about the effects of carbon monoxide on the fetus in utero. In that year Breslau[1] described carbon monoxide intoxication in 2 pregnant women from illuminating gas in a Zürich hospital. Both mothers survived. One was delivered of an apparently normal child, and the other had a stillborn, full-term fetus twenty-four hours after the carbon monoxide intoxication. In the latter case fetal movements had been observed before entry into the hospital, but no heart sounds could be elicited after the accident. Autopsy of the infant revealed that it had died from asphyxia about twenty-four hours before delivery. Two years earlier, in the same hospital, a pregnant woman had died from carbon monoxide poisoning. In the same year Freund[2] reported the death of a fetus in utero during the seventh month of pregnancy in a woman exposed to moderate carbon monoxide poisoning originating in a coal stove. Several people became ill, and the pregnant woman had severe headache, vomiting and chills. From then on she felt no fetal movements, and a month later she had a stillborn, macerated fetus. No abnormalities were found in either mother or child to account for the fetal death, which the author concluded to have been due, in all probability, to carbon monoxide although definite proofs were lacking.

The passage of monoxide gas from the maternal to the fetal circulation has been denied by some authors. Helpern and Strassman[3] report 1 and Martland and Martland[4] 2 cases of maternal and fetal death from carbon monoxide poisoning. High concentrations of carboxyhemoglobin were found in the maternal blood in these 3 cases, and the tissues showed the characteristic cherry-red color. The fetuses were cyanotic, with dark blood containing no carboxyhemoglobin. The authors concluded that the fetus does not die from carbon monoxide asphyxia, as the mothers did, but from simple asphyxia due to lack of oxygen that is normally supplied by the maternal blood through the placenta.

On the other hand Balthazard and Nicloux[5] report accidental carbon monoxide poisoning in a woman eight months pregnant who died whereas her husband and a baby, nine months old, survived. The mother's blood contained carboxyhemoglobin in a concentration of 16.9 vol. per cent (60 per cent saturation) and that of the fetus one of 4.6 vol. per cent (18 per cent saturation), indicating that carbon monoxide had entered the fetal circulation. Likewise, Dérobert, Le Breton and Bardon[6] determined the carboxyhemoglobin after death in 3 women, eight, three and two months pregnant respectively. The carboxyhemoglobin concentration in the blood of the woman in the eighth month of pregnancy was 15.3 vol. per cent, and that of the fetal blood was 2.2 vol. per cent. In the 2 cases of early pregnancy, the amount of fetal blood was not sufficient for examination, but their organs contained carboxyhemoglobin, although much less than that in the mother's tissues.

Eight cases were found in the literature[7-12] in which the mothers had carbon monoxide intoxication at various stages of pregnancy from the second month to near term. All the children showed a variety of psychomotor disturbances, when examined subsequently, such as mental retardment, in some cases amounting to idiocy, hypotonia of the neck, hypertonia of extremities, anatomic anomalies and hydrocephalus. Two of the infants died. Post-mortem examination of one, age six days, revealed hydrocephalus.[8] The other died nine days after birth from pneumonia, and autopsy showed extensive softening of the basal ganglions similar to that seen in adults with delayed death from carbon monoxide poisoning.[7] In all the cases with psychomotor disturbances in the children, the authors suggest a probable relation to the carbon monoxide poisoning of the mothers, presuming that carbon monoxide had passed through the placenta into the fetal circulation and caused injury especially to the central nervous system. The anatomic anomalies and psychomotor disturbances observed in

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these children have been correlated with the month of pregnancy when carbon monoxide intoxication of the mother occurred (Table 1).

Only 4 cases have been reported in which death of the fetus in utero followed exposure to carbon monoxide of mothers who survived. Two of these, occurring in 1859, have been referred to above.[1,2] The third case was presented by Tissier[13] in 1909. The pregnant woman had been in a gas-filled room for eight hours and was found in coma. She was immediately transferred to a hospital, and a few hours later she went into labor. Heart sounds of the fetus were absent. Eleven hours after arrival she was delivered of a stillborn infant presenting a rosy, fresh color, in contrast to the usual stillborn infant, so that artificial respiration was attempted. Post-mortem examination revealed the same carmine color of the tissues. Repeated spectroscopic examination of the blood of the fetus showed no carboxyhemoglobin. After extraction of the gas it was found that about a fifth of the hemoglobin had been replaced by carboxyhemoglobin.

In 1924 Phillips[14] reported the fourth death of a fetus in utero after carbon monoxide poisoning. A husband, a six-month-pregnant wife and a two-year-old child were accidentally poisoned during sleep from a leaking gas main. The child died whereas the two adults were resuscitated from coma and survived. No fetal movements were felt after the accident, and it was decided that the fetus was dead. Labor was not induced because the mother hoped that the child might be alive. Two months after the carbon monoxide poisoning she was delivered of a soft, flabby six-month-old fetus, weighing 0.9 kg., with a red skin and not macerated. Placenta and mother's blood contained no carboxyhemoglobin. A small amount of fluid in the chest cavities of the fetus contained carboxyhemoglobin, as determined by spectroscopic and other methods.

In a fifth case, presented below, the mother was exposed over a prolonged period to a concentration of carbon monoxide sufficient to cause symptoms of mild intoxication in the mother but resulting in the death of the unborn fetus.

TABLE 1. *Anatomic Anomalies and Psychomotor Disturbances in 8 Children, Correlated with the Month of Pregnancy in which Carbon Monoxide Poisoning of the Mother Occurred.*

Stage of Pregnancy	Mongolism	Microcephaly	Hydrocephalus	Softening of Brain	Retraction of Inferior Maxilla	Ptosis of Tongue	Precocious Development of Breasts	Strabismus	Delayed Dentition
	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases
mo.									
2	1								
3					1	1	1		
4		1							1
5			1†					1	1
7								1	
8			1‡						
8½				1§					
Totals	1	1	2	1	1	1	1	2	2

*No voluntary movements; tremor of legs & twitching of arms on percussion.
†Determined by encephalography.
‡Death at 6 days of age.
§Determined at autopsy, death at 9 days of age.

Case Report

H.N. (N.E.H. 119970), a 21-year-old primigravida, was followed during her pregnancy in the ante-partum clinic of the New England Hospital. The expected date of confinement was December 25, 1950. Fetal movements were felt from 4½ months on, and with the exception of persistent nausea and vomiting the pregnancy until the last month was uneventful. The blood pressure remained within normal limits, and examinations of the urine showed no albumin. Mild nausea and vomiting persisted in spite of regulation of the diet and administration of Dramamine and pyridoxine. On the last prenatal visit on November 16, she stated that the baby was less active than before, and the fetal heart, which had been heard in the left lower quadrant, ranging from 144 to 148 per minute, was now about 128, in the right lower quadrant and irregular. The patient failed to keep her appointments after that because of an upper respiratory infection.

On December 22, the evening before admission to the hospital, she and her husband visited at the home of friends. After an hour and a half the patient began "feeling dizzy" and vomited. At that time she noted a sudden increase in fetal activity, followed by complete absence of movements. The patient's husband and 3 other members of the household, including a 3-year-old child, had symptoms of nausea, vomiting and headache. One of these allegedly lost consciousness for a brief period. The patient remained in this house overnight. On the following morning both she and her husband noted headache, nausea and unsteadiness of gait. The other members of the household were reported sleeping soundly and somewhat difficult to arouse. The patient's husband stated that there was an odor of gas throughout the house and that a combination gas and oil stove had been burning in an adjoining room through the night. The patient continued to have nausea and vomited during that

day. Labor began in the evening, and she was admitted to the hospital in active labor. She complained of symptoms of an upper respiratory infection and nausea and vomiting, which had become much worse during the past 24 hours. No fetal movements had been felt since the previous evening.

Physical examination showed a young, very apprehensive woman who was belching frequently and complaining of nausea. The temperature was 99.4°F., the pulse 90, and the respirations 24 per minute. The blood pressure was 110/80. The hemoglobin was 12.3 gm. per 100 cc., and the red-cell count 4,130,000; the white-cell count was 23,800, with 90 per cent neutrophils (including 14 band forms), 9 per cent lymphocytes and 1 per cent monocytes. There was a bright flush of the face, and a faint pink, macular eruption over the back. The fetal heartbeat was not audible. The cervix was dilated to admit 1½ fingers, and contractions occurred at 2-minute intervals. She was given the customary barbiturate, Demerol and scopolamine analgesia, and after 5½ hours of labor was delivered of a stillborn fetus by low forceps, under nitrous oxide and ether anesthesia.

Post-mortem examination revealed a well formed, newborn female infant measuring 48.5 cm. in length and weighing 2800 gm. The skin on the limbs was partly macerated. The skin of the body otherwise was white except for bright-red mottling over the arms and legs and a reddish flush over the back. The nail beds, lips, cheeks, conjunctivas, ears and the caput of the scalp were brilliantly red. The leptomeninges of the brain and the serous surface of the body cavities showed the same color. The pleural, pericardial and peritoneal cavities contained a small amount of blood-tinged fluid. Petechial hemorrhages were present in the epicardium, the pleurae, the pelvic mucosa of the kidney and the choroid plexus of the lateral ventricles, and in the cerebellar subarachnoid space. All the organs showed generalized congestion. The rotation of the intestine was incomplete. No other congenital abnormalities were found.

On analysis of blood removed from the vena cava* the color suggested the presence of carbon monoxide. Aliquots of this specimen and of normal blood were prepared and carefully balanced in the microspectroscope. The reducing agent used was ammonium sulfide. After addition of the reducing agent the normal specimen gave the single broad band of hemoglobin, but the case specimen still showed the persistent 2 narrow bands indicating the presence of carbon monoxide.

According to the examiner a saturation of carbon monoxide of less than 20 per cent is not distinguishable from normal blood, and in the range of 20 to 25 per cent close observation shows a darkening between the carbon monoxide bands. Thus, the positive qualitative test indicates a concentration greater than 25 per cent saturation.

The next day, a quantitative analysis was made on the case specimen by means of a Van Slyke blood-gas apparatus of volumetric type. Carbon dioxide was absorbed with sodium hydroxide solution; oxygen was absorbed with an alkaline solution of sodium hydrosulfite and sodium anthraquinone-beta-sulfonate; and carbon monoxide was absorbed in an alkaline solution of cuprous chloride and ammonium chloride.

Hemoglobin was determined by calculation from an iron analysis (Wong's method) with further calculation of carbon monoxide capacity. The following values were obtained: carbon monoxide, 10.8 vol. per cent; saturation, 49 per cent; hemoglobin, 16.4 gm. per 100 cc.; carbon monoxide capacity, 22.0 vol. per cent; and cell content, 57 per cent.

The percentage saturation was calculated by division of the value of carbon monoxide observed (in volumes per cent), times 100, by the carbon monoxide capacity.

*Examined in the Medical Examiner's office by Mr. Frank Stratton, Boston police chemist and assistant in legal medicine, Harvard Medical School.

TABLE 1 *(Concluded).*

STAGE OF PREGNANCY	HYPOTONIA OF NECK MUSCLES	HYPERTONIA (SPASTICITY) OF LIMBS	INVOLUNTARY TREMOR & TWITCHING[9]	CONVULSIONS	ATHETOSIS	ABSENT CRY & SUCKING REFLEX	DEFECTIVE OR ABSENT SPEECH	INCONTINENCE	LOW MENTAL LEVEL	IDIOCY
	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES
MO.										
2										
3	1	1							1	
4	1	1				1	1	1		1
5		1		1			1			1
7		1		1						
8		1			1					
8½			1			1				
Totals	2	5	1	2	1	2	2	1	1	2

DISCUSSION

Whether carbon monoxide can enter the fetal circulation and cause death or injury of the fetus is a question that has caused considerable disagreement. Theoretically, a diffusible gas like carbon monoxide could probably cross the placental barrier with the same ease as oxygen. In the opinion of some authors[3,4] this does not occur because of the marked affinity between carbon monoxide and hemoglobin. The mother dies before all her cells are saturated and before diffusible carbon monoxide in the plasma reaches the placenta, and red blood cells, saturated with carbon monoxide, do not cross the placental barrier. The fetus dies from simple anoxia due to lack of oxygen. This opinion is also voiced by others[5,12] provided that the mother is subjected to acute poisoning with large doses of carbon monoxide so that she dies in a short time. However, when the mother

dies from a moderately large dose continued over a longer period, small amounts of carboxyhemoglobin are demonstrable in the fetal blood.[5,6]

A possible mechanism by which carbon monoxide is transferred to the fetal blood is suggested by Nicloux[15] and reiterated by Dérobert, Le Breton and Bardon.[6] In their opinion the erythrocytes probably do not constitute the only tissue that fixes the carbon monoxide. Some of the gas remains in the plasma, and an equilibrium is gradually established between carboxyhemoglobin and intracellular and interstitial fluid at the placental level. Carbon monoxide then passes the placental villi like other gases and nutrient materials. This equilibrium depends on the duration of the maternal intoxication and the constancy of concentration in the maternal blood. If either of these factors is low no equilibrium is established, and it is never realized in rapid, acute carbon monoxide poisoning.

The theory that the plasma is the conveyor of carbon monoxide was proved by Nicloux[15] in an in vitro experiment. He suspended a cecum from an ox filled with blood containing carboxyhemoglobin in a glass of physiologic saline solution and placed a fish in the glass. After two hours the fish was killed, and it was found that its blood contained carbon monoxide. The saline liquid remained clear throughout.

The opinion of Nicloux, based on experimental work, that slow intoxication with moderate doses of carbon monoxide is the condition that will cause death of the fetus with survival of the mother is supported by Tissier.[13] He reported the only death of the fetus in utero with analysis of the fetal blood, which was 20 per cent saturated with carboxyhemoglobin. Since the mother in this case had attempted suicide and had been found in coma, death of the fetus may have occurred early and in part been due to lack of oxygen or a marked sensitivity of the fetus to carbon monoxide.

In the case reported above, in which the mother was exposed to carbon monoxide long enough and in sufficient amounts to cause symptoms, but not death, sufficient carbon monoxide did diffuse from the maternal to the fetal circulation to produce 49 per cent saturation of the fetal hemoglobin and cause the death of the fetus. With cessation of the circulation of the fetus, the carboxyhemoglobin was not eliminated from the fetal blood. Probably, the fetus is more sensitive to carbon monoxide poisoning and requires smaller doses than the accepted 65 per cent saturation for adults. This case proves conclusively that carbon monoxide may enter the fetal circulation under certain circumstances and cause death.

In the 8 cases in the literature in which living children with psychomotor disturbances were born to mothers who at some time during pregnancy had been exposed to carbon monoxide poisoning, a causal relation is possible. However, the degenerative changes found in the central nervous system of 1 infant who died[7] may be found in simple anoxia and other toxic states.[8]

Summary

A case of intrauterine death of a full-term female fetus due to asphyxia caused by accidental, long continued, nonfatal carbon monoxide poisoning of the mother is reported.

The typical cherry-red color of skin and organs of the fetus was present, and fetal blood was 49 per cent saturated with carboxyhemoglobin.

Twenty-three cases collected from the literature on carbon monoxide poisoning during pregnancy are reviewed.

We are indebted to Dr. Richard Ford, Department of Legal Medicine, Harvard Medical School, and his staff for the examination of the blood and valuable suggestions in the preparation of the manuscript.

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MEDICAL PROGRESS

ORAL MEDICINE

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IN the preparation of this progress report on oral diseases, primarily concerning the oral mucosa, we were impressed by the paucity of literature dealing with the mouth as an entity. Much of the literature consists of reports of clinical cases of general interest such as a reaction to a drug with oral manifestations.

During the past decade the dental and dermatologic journals have furnished most of the information that one might refer to as progress in the subject of oral medicine. Many lesions involving the mucous membrane of the mouth, other than discrete lesions from local causes such as leukoplakia buccalis, are related to disease elsewhere in the body. One cannot separate the oral cavity from the body as a whole, and the mouth may thus be regarded as the diagnostic mirror of the body.

On reviewing the progress of knowledge of oral diseases, we have refrained from including purely dental conditions, periodontal disease, bone lesions, neoplasms and surgical inflammatory processes.

Oral medicine as a subject taught in dental schools is relatively new, and about two thirds of the dental schools in the United States have provided instruction as a single course. In a recent visit to Canada we noted that the seven dental schools have not, as yet, instituted a course in oral medicine as a part of the curriculum.

Studies in viral diseases have only recently contributed criteria to differentiate various inflammatory lesions of the oral cavity; the reactions from various antibiotics represent another recent addition to the knowledge of oral disease.

Mechanical local factors, together with psychosomatism, are important in the etiology of mouth lesions formerly clouded in obscurity. Mechanical factors represent the all-important cause of focal mucous-membrane lesions. Too often, local irritations due to faulty occlusion, imperfectly fitting dentures, both partial and full, dental caries, crowns and clasps from bridges and habit biting are overlooked, and other causes are needlessly sought as etiologic factors. Except for frictional irritation from both partial and full dentures, we do not believe that plates are chemically active and responsible for the so-called denture sore mouth.

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DENTURE SORE MOUTH

Among the many articles on mechanical traumatic conditions of the oral cavity commonly referred to as "denture sore mouth," a study of this condition by Nyquist[1] merits a review of his investigations.

The appearance, beneath artificial dentures, of chronic inflammatory changes of the oral mucosa is frequent. The denture-covered area becomes edematous, presenting either an erythematous smooth surface or, in most chronic cases, granulation tissue, often seen opposite the now obsolete vacuum chambers. The tongue is sometimes involved with erythema and edema, often with considerable discomfort and pain along with disturbances of salivation. These pathologic changes of the oral mucosa, the origins of which are traceable to the presence of the dental plate, are mentioned in the literature under many different names. Examples of these terms include stomatitis prosthetica, stomatitis nudata, stomatitis venenata, stomatopathia allergica, rubber sore mouth and denture sore mouth.

In the available literature covering half a century a number of principal causal factors are mentioned. The first of these consists of nonphysiologic conditions, explained on the basis that every denture sets up abnormal conditions in the mucosa, resulting in disturbances of the blood circulation, secretions and self-cleansing capacity. The second group comprises traumatic injuries (during chewing and speaking, the plate makes some movement against the mucosa, and in certain cases, poor surface, marginal fit and traumatizing occlusal relations that cause some displacement between mucosa and plate are also found, and any resulting injury to the mucosa is purely traumatic. The third is heat accumulation: base materials of low thermal conductivity, such as rubber and various kinds of synthetic resins, may give rise to an accumulation of heat in the plate. The permanently raised temperature may conceivably have a deleterious effect on the mucosa. A fourth condition is putrefaction — poor oral hygiene and inadequate cleansing of the plate set up conditions whereby food particles, desquamated cells and inspissated secretions provide a favorable medium for the oral bacterial flora that may cause inflammatory reaction of the mucosa. A fifth group includes chemicotoxic injuries; the base material itself or its constituents, such as dyes, stabilizers and accelerators, may cause chem-

icotoxic injury to the mucosa. A sixth is composed of allergic reactions of the mucosa: the base material or its constituents may give rise to allergic reactions of the mucosa. Cleansing materials for the plate may have a similar effect. Finally, vital resistance may be depressed because of systemic disease: such conditions as diabetes, nephritis, anemia, leukemia, vitamin deficiency and hormonal disturbances are considered factors reducing the vital resistance to trauma of the oral mucosa. Inflammatory changes may thus arise more easily.

In the study of the traumatic group of cases it was concluded that trauma in its various forms plays a great part in the occurrence of dental sore mouth. The types of trauma considered were instability, traumatizing centric occlusion and traumatizing articulation. This study gave rise to the establishment of an "ideal group" consisting of cases of good stability, correct centric occlusion and balanced articulation, and groups comprising the different types of trauma, occurring either singly or in combinations.

The frequencies of dental sore mouth for the different groups were as follows: ideal group, 2 per cent; one traumatic factor, 15 per cent; two traumatic factors, 50 per cent; and three traumatic factors, 75 per cent.

Trauma thus appears to be the dominating factor in the occurrence of dental sore mouth and its variation in frequency.

The use of the patch and mucosal-contact tests, as applied in Nyquist's[2] experiment, has virtually ruled out the probability that dental sore mouth is allergic. In the test for possible hypersensitiveness to the denture base materials, the finely pulverized grindings, which were not taken from the surface layer of the suspected denture, were used as a test substance. In the mucosal-contact test the base material as such served as the test substance in a number of cases.

In one method the contact between the denture base and the mucosa was broken by covering of the membrane side of the denture with tinfoil. When the mucosa had clinically healed, the foil was removed so that the oral mucosa was re-exposed to the base material.

In another method the contact between the base material and the mucosa was retained, but trauma was eliminated through careful selective grinding of the denture.

Nyquist's chief conclusion, drawn from his investigation, was that trauma is the predominating cause of denture sore mouth. A hypersensitiveness of the oral mucosa against some constituent of the dental base, with subsequent allergic reaction, is also conceivable, but the frequency of such injuries is probably quite low. The possibility cannot be excluded that dental sore mouth is also a toxic effect arising, for example, from a free monomer in an acrylic resin.

Our observations over a prolonged period in patients wearing dentures concur with Nyquist's experimental investigations that frictional trauma is the all-important factor.

In older persons, more often women, inability to adjust themselves to the wearing of dentures is not uncommon. When definite mechanical factors are involved they can usually be remedied. Psychosomatic factors play an important part among older women although xerostomia, which is due to diminished salivary secretions associated with atrophy of the oral mucosa, creates a real problem in these cases. Intermittent pressure from dentures on a dry mucous membrane frequently stimulates a verrucous or papillomatous reaction of the mucosa.

Electrogalvanism

A subject much discussed up to a decade ago has ceased to attract attention in recent years, and the literature dealing with this phenomena has been practically nonexistent of late.

Lain,[2] Ganowsky,[3] Campbell[4] and others stress the importance of electrolytic lesions of the mouth, caused by the effect of galvanic currents that arise in the oral cavity from dissimilar metals in the presence of saliva.

Lain and Caughron,[5] in their article, give in detail a theory of electrogalvanism as a cause of important lesions of the oral mucous membrane. In explanation, they state that human saliva contains the necessary elements for a good electrolyte, whether its chemical reaction is neutral, acid or alkaline. Therefore, a galvanic battery is constructed in every oral cavity where restoration has been made from two or more electropotentially dissimilar metals. The common subjective symptoms of the electrochemical changes in the mouth are metallic or salty taste, increased salivary secretion and a burning or tingling sensation, usually occurring on the margin of the tongue. The objective signs include disintegration and discoloration of metallic restorations, revealed by a dark, tarnished color, which is the result of sulfides and other ionized products that have migrated from the positive metals such as aluminum, zinc, nickel and copper through the saliva to be deposited on the electronegative gold, platinum or silver restorations. Evidence of chronic irritation, with erosions and ulcers on the dorsal area of the tongue as well as leukoplakia, is said by these investigators to be caused by these phenomena. Cases of electrogalvanism are reported to improve at once, and all lesions, except leukoplakia, heal promptly after removal of restorations of either the positive or the negative group. The authors state that, when the lesions have healed, new restorations made from homologous metals guarantee against recurrence. For making electric estimations of potential damage to tissues, they used a Weston microammeter with a range of 75 microamperes.

Reed and Willman,[6] in their discussion of the sub-

ject, indicate that galvanic currents in the oral cavity have been reported for eighty years.

From the electrochemical point of view, three different combinations of dissimilar metals can occur in the mouth: dissimilar metals that never come in contact; dissimilar metals that are always in contact; and dissimilar metals that are intermittently in contact in mastication.

On the basis of their experiments, they conclude that the presence of two or more dissimilar metals that are not in contact cannot give rise to galvanic currents. They further interpret the experiments as demonstrating that the intensities of galvanic currents between dissimilar metals that are in direct contact are lower than 1 microammeter. Galvanic currents of this order have not been considered harmful by previous authors.

Schriever and Diamond[7] performed experiments on electromotive forces and electric current caused by metallic dental fillings. They described the sources of possible electromotive forces for pairs of metallic fillings and for single fillings. A condenser-ballistic-galvanometer-potential-difference meter was developed with which the differences in electric potential between pairs of metallic fillings could be measured. They concluded that serious pathologic conditions in the oral cavity have been caused by metallic fillings and also that the bone fluid is just as important as the saliva in causing electric currents.

This is an excellent piece of research indicating possible sources of electromotive activity for electromotive forces for single and pairs of metallic fillings. However, in our experience, the absence of mucosal lesions that can be related to these electric phenomena suggests that, from a practical standpoint, they can be ignored as causes of lesions of the oral mucous membrane.

We have had the opportunity of studying a large group of so-called electrogalvanic lesions involving the oral cavity and have satisfied ourselves that other factors such as rough surfaces of restorations, faulty occlusion, poorly fitting dentures and irritation from other mechanical appliances best explain the lesions involving the oral mucous membrane. If the dental profession accepted the explanation of oral galvanism as a cause of these "galvanic burns" and leukoplakia, it would represent a herculean task on their part to drill and replace the dental fillings of different potentialities now existing in oral cavities of the many million inhabitants in this country.

Viral Disease

Perhaps in no other field of oral medicine have the advances in diagnosis and classification been so outstanding and sound. Of course, the introduction of such new diagnostic tools in the study of viruses as the electron microscope, serologic technics and cultural methods brought about an inevitable amount of investigative work in this field. The herpes virus was the first organism to feel the full impact of research minds, and names like Dodd, Scott and Blank have now become synonymous with the brilliant work with this virus. The first great clinical study was presented by Dodd, Johnston and Buddingh,[8] which definitely defined the entity of herpetic stomatitis in children. This was followed by the classic study of Scott, Steigman and Convey,[9] which clarified the entity still further. The most recent investigation, by Buddingh et al.,[10] gives more information about the natural course of this disease. We have seen numerous cases in children and, occasionally, in adults, and the same pattern is followed in most cases. There is a fairly acute onset with the rapid development of discrete, uniform, vesicular lesions accompanied by pronounced systemic manifestations. Although there are numerous enthusiastic reports concerning the efficacy of wide-spectrum antibiotics, we have not been impressed with any significant effect in our cases. Of course, none should be expected, especially in the light of the work of Baldridge and Blank,[11] which showed conclusively that chlortetracycline had no effect on the virus of herpes simplex in embryonated eggs. We resort only to local soothing measures, combined with general treatment, to relieve pain and correct diminished food and fluid intake. On recovering from the stomatitis the patient is left with a high antibody titer to the herpes virus that will protect him from any further primary infection. However, he may still be plagued with recurrent herpetic infection of the lips and other mucous membranes or skin areas. We have seen recurrent herpes-simplex infections follow a variety of immediate causes such as trauma, sun exposure and febrile disease. One of the most widely recommended means of therapy — namely, repeated smallpox vaccination — is without any scientific basis. There is no immunologic relation between the herpes and vaccinia viruses. The neutralizing antibody titer in patients suffering from repeated herpetic infection is already high, and no alteration follows such a procedure. If, by chance, any success results from the vaccination, it is perhaps from the psychotherapeutic effect. We have been impressed with emotional influences in recalcitrant recurrent herpetic infections. This concept is not new,[12] and a sympathetic understanding approach to these patients will often accomplish much more than a myriad of vaccinations, antibiotics and other nonspecific therapeutic attempts.

Herpangina is not a new viral disease of the oral cavity, for it was first described by Zahorsky[13] in 1920. However, it remained as an obscure entity until 1951, when an excellent study[14] solved the etiologic, immunologic and epidemiologic problems of this disease. It is somewhat similar to acute herpetic gingivostomatitis except that it runs a much milder course and only the posterior aspect of the oral cavity is involved. Probably, most of these cases are overlooked or disposed of as a streptococcal sore throat or ton-

sillitis. It is due to the coxsackie virus, Group A, and, like the herpes virus, does not respond to any specific antibiotic therapy. The usual course of the disease is only four to seven days, and the constitutional symptoms are mild. Only conservative symptomatic therapy is recommended.

There has been little progress to report on other viral diseases affecting the oral cavity. Hoof-and-mouth disease is rare in this country, and most of the reports are in the foreign literature. Herpes zoster, verruca vulgaris, molluscum contagiosum and orf are all very rare. We have seen several cases of accidental vaccination, involving the lips; the diagnosis should be thought of in children who have recently been vaccinated or who have been in contact with recently vaccinated children. The lesions can be extremely inflammatory and mimic primary syphilis, neoplastic disease or severe deep pyoderma or fungous disease.

Aphthous Stomatitis

This is one of the most frequently encountered diseases in oral medicine, and yet it remains one of the least well understood. Despite numerous reports involving the herpes virus, as well as other undiscovered viruses, the etiology remains unknown. From a review of the literature on this subject there appears to be an almost universal acceptance of the concept that aphthous stomatitis is ushered in by a vesicle that ruptures, leaving an eroded surface similar to the natural development of lesions due to the herpes virus. We have purposely followed patients with recurrent aphthous stomatitis at daily intervals to observe the initial lesions. In no case were we able to see a vesicle. Instead, a macular area of erythema appeared initially, followed by slight induration, color changes and a slough of the involved mucous membrane, leaving a well defined ulceration whose base became covered with a grayish membranous exudate. The whole process resembled what one might expect from a minute infarction of the area. Stark, Kibrick and Weisberger,[15] in their series, confirmed this observation.

The first conclusive proof that the herpes virus was not the etiologic agent for this disease was forthcoming from Blank et al.,[16] who demonstrated that aphthous lesions histologically do not show inclusion bodies or any other evidence of a viral etiology. Furthermore, the herpes virus could not be cultured from any of the lesions, and the herpes-simplex-neutralizing-antibody response was not altered by the course of the disease. Stark and his associates[15] gave further proof with the herpes-simplex complement-fixation antibody studies, which again failed to show any relation to the development of aphthous stomatitis.

The location of the lesion is extremely variable, the vestibule of the oral cavity being the most frequent site in our experience. The average course is about two and a half weeks although considerable differences are noted. One to four are the average number of individual lesions. Therapy remains a difficult problem, and what we have said regarding the treatment of recurrent herpes labialis can be repeated for this condition.

Kutscher, Silvers and Zegarelli[17,18] have contributed considerable information by their controlled studies demonstrating the failure of smallpox vaccination, antibiotics and antihistamines in the treatment of aphthous stomatitis. In severe cases, when there is considerable discomfort and disability, we have used hydrocortisone orally in moderate doses. Although it has been extremely useful in some cases, we certainly do not recommend this as a routine therapeutic agent, and when it is discontinued, new attacks can occur. Many of the cases that we observe are in emotionally fatigued young people. Often, the attacks occur during an acute emotional upset. Therapeutic efforts in the direction of relieving emotional tension, along with general supportive measures, have appeared to bring the most gratifying results.

Bullous Diseases

For many years bullous diseases of the oral cavity have caused great concern, not only as an immediate problem of discomfort to the patient but also as a challenge to the clinician in therapy, diagnosis and prognosis. In this country there was great confusion and inability to differentiate erythema multiforme bullosum from pemphigus in the early stages five or six years ago, and yet, in 1943, Civatte[19] eruditely described histologic changes that he considered diagnostic of pemphigus; in 1948 Tzanck[20] showed how a simple tissue smear could help make a positive diagnosis of pemphigus. However, it was not until Blank[21] and Lever[22] presented their reports that the recognition of the European work was universal.

Erythema multiforme bullosum represents the most common group of bullous eruptions of the oral cavity. We look upon it more as a symptom complex than as a disease entity, and as knowledge broadens, more and more causes for this reaction may be found in the mouth and skin. We agree with Robinson and McCrumb[23] that Stevens–Johnson syndrome, ectodermosis erosiva pluriorificialis, and Behçet's and possibly Reiter's disease are all a manifestation of a single entity—namely, erythema multiforme exudativum.

We are aware of drug sensitivities producing this picture, and undoubtedly there are other mechanisms that remain obscure. Erythema multiforme is usually a self-limited disease. Its course is extremely variable and may be mild or severe and even fatal. We attempt to elicit carefully a history of ingestion of drugs and to eliminate any suspected offenders. In severe cases ACTH and cortisone are usually very helpful and can be life saving. Histologic study

demonstrates a nonspecific reaction consisting of a subepidermal bulla with inflammatory exudate.

Pemphigus is a potentially fatal disease of unknown etiology characterized by epidermal changes leading to the formation of bullae. There are four types of the true malignant forms: pemphigus vulgaris; pemphigus vegetans; pemphigus foliaceus; and pemphigus erythematosus (Senear–Usher). There are also three chronic, more benign types: chronic benign mucous-membrane pemphigus; benign chronic familial pemphigus of Haley and Haley; and bullous pemphigoid (perhaps a variant of bullous dermatitis herpatiformis or erythema multiforme bullosum). Oral lesions are found in every case of pemphigus vulgaris and are frequently the initial lesion. They are also usually seen with pemphigus vegetans but less frequently with pemphigus foliaceus and erythematosus. Benign mucous-membrane pemphigus is almost always accompanied by oral lesions; in all the patients that we have studied they were present, and frequently they were found in no other areas. Oral lesions are a prominent part of bullous pemphigoid. We have never seen mucous-membrane lesions in benign chronic familial pemphigus.

There is nothing characteristic about the lesions in the oral cavity encountered in these various diseases. The bulla is extremely short-lived owing to a thin wall and the traumatizing elements that prevail in the oral cavity. Therefore, one must evaluate the entire clinical picture and employ the necessary laboratory procedures, especially tissue smears and biopsies. The histologic picture of true pemphigus is diagnostic. The two most important and pathognomonic elements are the position of the bulla—intraepidermally—and the presence of acantholysis; the acantholytic cells may also be seen in the tissue smears as described by Tzanck.[20]

Therapy has been revolutionized by the advent of ACTH and cortisone. Before their use a diagnosis of pemphigus vulgaris was a sentence to a miserable death with ulcerating lesions, malnutrition and general debility. Although these drugs are not curative, they effect remissions for varying lengths of time, and maintenance doses are often effective. There are no new advances in etiology, but one must be thankful for the important forward steps in diagnosis and therapy of this dreaded disease.

Leukoplakia Buccalis and Oral Cancer

The recent definite increase of cancer of the lung, with evidence of its relation to the inhalation of the products of combustion from cigarettes, has tended to divert the attention of the medical and dental professions from the frequent occurrence of oral carcinoma found in heavy pipe smokers. As a result of the unfavorable publicity attached to the apparent relation between the smoking of cigarettes and lung cancer some have suggested that if one feels the need for smoking, it would be more desirable to turn to the cigar or the pipe as the least harmful. The inhalation of smoke is very much less frequent in one who enjoys these forms of smoking. We call attention to the fact that it is impossible to determine all the early curable pulmonary processes of cancer even with routine x-ray examination. In contrast one can observe the premalignant lesions of leukoplakia and early carcinoma, readily visible and often found in heavy pipe smokers. In spite of the fact that early lesions of carcinoma of the mouth can be detected, more than 4000 persons die of oral carcinoma annually in the United States. A switch from cigarettes to the cigar or pipe may reduce the frequency of cancer of the lung and in turn cause an increase in oral carcinoma. In discussing this extremely common and premalignant lesion—namely, leukoplakia buccalis—we can state that it is the most common in importance of the mouth lesions, numbering 15 per cent of a collected group of 4728 patients.[24] In a report of 316 cases[25] of leukoplakia, and again a total of 671 patients[24] with leukoplakia buccalis, there was evidence that the products of combustion of tobacco, particularly in pipe smokers, often combined with local irritation, represent the important factors in the production of oral carcinoma. Probably, an additional factor is present in most cases in which the cancers develop in the older age group—namely, the loss of tissue resistance related to a hormonal inactivity. This suggestion is difficult to prove by experimental investigation.

Our experience in the sex distribution of oral carcinoma is in agreement with that of others—only 10 per cent of cases occur in the female and usually in the later decades of life. Many of the cases of carcinoma in aged women are found in edentulous mouths and are due to irritation of ill fitting dentures, with frequent involvement of the tongue.

(To be concluded)

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MEDICAL INTELLIGENCE

MOUNTAINEERING PHYSICIANS

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OF all the activities of physicians, other than the practice of their chosen profession, mountaineering is perhaps the most fascinating and hazardous. In spite of its perils, doctors have long been drawn to this arduous pursuit, some for the pure pleasure of climbing and others taking the part of medical officers to official expeditions. In some cases, indeed, they have been the actual leaders of exploring parties. Of those who have climbed primarily for pleasure, none are more noteworthy than William Howard and Jeremiah Van Rensselaer, young American medical graduates who topped Mont Blanc in 1819, and Clinton Dent, an English physician, who overcame in 1878 the formidable difficulties of scaling the Aiguille du Dru, one of the unique rock needles of the Mont Blanc chain, after eighteen previous attempts had failed.

William Howard, a graduate of the University of Maryland in the class of 1817, made the ascent of Mont Blanc in the summer of 1819, accompanied by a fellow physician, Jeremiah Van Rensselaer, who had received his degree from the University of New York, also in 1817. Both had been on a grand tour visiting medical centers in Europe and in Italy had climbed both Etna and Vesuvius before they crossed the Alps into Chamonix. Mont Blanc was a natural lure, and the two young physicians stood on the top, after an uneventful ascent, on July 12, 1819, the first Americans to do so. On the return journey they suffered from snow blindness, but otherwise do not appear to have been seriously affected by their adventure to a height of 15,781 feet.

The climb had, of course, been accomplished before 1819—the first time, indeed, by another physician, Michel-Gabriel Paccard, the local doctor of Chamonix, who in 1786 scaled the top with one guide, a feat considered by most authorities today as the most important event in the history of mountaineering. It was this same kindly physician who advised Howard and Van Rensselaer before their ascent in 1819.

Howard's account, *A Narrative of a Journey to the Summit of Mont Blanc . . . July 1819* (Baltimore, 1821; second edition, 1856), is chiefly remembered for his description of the moonlight view from his overnight camp near the top. The spectacle was, he wrote, so sublime as to render him for a time, "insensible to all feelings of personal suffering. The sky was very clear, but perfectly black; the moon and stars, whose rays were not obscured by passing through the lower dense region of the atmosphere, as when seen from the surface of the earth, shone with a brilliancy, tenfold of what I had ever observed from below: and the comet with its bright tail formed, in the northwest, a beautiful object." A commonplace now that such a view 3 miles above the earth is well known to every aeroplane passenger who travels by night. To Howard, the clearness of the atmosphere gave each star, like those in Shakespeare's imagination that "i' th' darkest night stick fiery off indeed," and heightened his "feelings of awful sublimity, which our situation was so calculated to inspire." The young Baltimore physician was amazed, as many have since been, by the dark indigo of the actinic sky, and he felt that emotional uplift, so common in flyers today, that comes from the semidetachment from earthly entanglements, augmented by the satisfaction of accomplishment and an almost overwhelming sense of freedom and oneness.

If Howard was uplifted by his ascent of the more simple Mont Blanc, how much more gratification must have come to Clinton Dent when he topped the Aiguille du Dru nearly sixty years later! With J. W. Hartley, he made this difficult rock climb in 1878, nearly a hundred years after Paccard had looked down on Chamonix from atop Mont Blanc. But the Aiguille du Dru was more formidable, although not so high. It stands out like a needle in the broken line of the Mont Blanc chain, as seen from Montenvers, above Chamonix, and Dent, who had gazed up to it as a "holiday dream of five years," could only exclaim from the peak: "Where in the wide world

will you find a sport able to yield pleasure like this?" And yet, for a second or two, "all of the past seemed blotted out, all consciousness of self, all desire of life was lost, and I was seized with an impulse almost incontrollable to throw myself down the vertical precipice which lay immediately at my feet." "I know not now," he wrote later, "though the feeling is still and always will be intensely vivid, how it was resisted, but at the sound of the voices below the faculties seemed to return each to its proper place, and with the restoration of the mental balance the momentary idea of violently overturning the physical balance vanished." Hamlet, climbing the peaks of mental anguish, had many such a "momentary idea," recalled too by the sound of a voice, when the faculties returned "each to its proper place." Such is the fabric of high emotional experience, seldom vouchsafed common man, but inherent in stories of the mountaineers and those that make great effort to overcome material or spiritual obstacles.

Other physicians in the next hundred years followed the trail of Paccard, Howard and Van Rensselaer up the slopes of Mont Blanc: Edmund Clark, of London, in 1825; Martin Barry, of Edinburgh, the embryologist, in 1834; Harry Allen Grant in 1839; Edouard Ordinaire in 1843; Auguste Lepileur in 1844; Albert Smith, the English country practitioner who abandoned medicine for journalism, in 1851; and Israel Tisdale Talbot, of Boston, in 1854, to mention only a few who reached the top. In those days the climbs were largely sporting ascents, without extensive scientific observations, as came to be more or less the rule in later expeditions on this and other mountains. A few key observations, however, were made, many of them ignored by later climbers, sometimes with fatal consequences. Clark, for instance, noted that the firing of a pistol contributed to producing an avalanche, which fell shortly after. A guide, falling asleep over a charcoal brazier was overcome by carbon monoxide, an event that has frequently led to disaster to explorers, both mountaineers and others. Clark and Barry gave descriptions of mountain sickness, and the latter came near exhaustion at the summit. Barry, who had studied with Tiedemann at Heidelberg and later with Purkinje at Breslau, was the most distinguished of the early physicians to climb Mont Blanc, and his scientific observations on insect life, barometric pressure and geology were of considerable value. Ordinaire's ascent is of interest, for he reached the top on August 25-26, 1843, and repeated his climb after only a few days of rest on August 30-31, but except for his demonstration of man's endurance, he does not seem to have been more than a holiday tourist, thoroughly enjoying his triumphs. Lepileur, on the other hand, made a purely scientific ascent, his party remaining on the mountain for a number of days making meteorologic and geodetic surveys. They attained the summit on August 29, 1844. Albert Smith, son of an English surgeon, spent a summer at the Hôtel Dieu in Paris and on a walking holiday got his first view of Mont Blanc in 1838; but he did not ascend until 1851 after he had abandoned medicine for journalism. On his return to London, he began some lectures that caught the public fancy. These ran in Egyptian Hall, Piccadilly, until his death in 1860, there being nearly 200,000 admissions in the two seasons of 1852 and 1853. More than 2000 performances were given, and many an Englishman was inspired by Smith's engrossing story to adopt mountaineering as a sport. His account, published in 1853, is marked by dignity and charm. He was an author of note, contributing to *Punch* and writing novels and extravaganzas. Although he made no scientific contribution to mountaineering, Smith was enormously successful in popularizing the sport of climbing. Israel Talbot, who made the second complete ascent by an American in 1854, followed Albert Smith's idea of climbing as a sport. He had ascended Mount Washington in 1853, and the next year, after graduating from Harvard Medical School, when on top of Mont Blanc on August 25-26, dropped a pebble carried from the top of Washington, the "Mont Blanc of America." He later became professor of surgery and dean at Boston University School of Medicine.

The first and only American physician to meet his end on Mont Blanc was James Baxter Bean, who, with a Scotch clergyman, was lost in a snowstorm in 1870, not far from the summit. His body and the corpses of his friend and their three guides were all recovered the same year, but an ice axe with Bean's name inscribed on the shaft was not found until fifty-seven years later, thus closing the evidence of Mont Blanc's worst disaster.

With the passing of time men have climbed higher and higher until the Himalayan giants have been overcome — even Everest, in 1953, by a large expedition equipped with every aid, including the use of oxygen. But rarely is the summit won on the first major attempt, for many obstacles must be overcome before the goal is achieved through the skill, judgment and courage of a team. In such a group a physician may be indispensable, and in some instances, such as the 1953 attack on Karakoram or K2, the second highest mountain in the world, the leader may be a member of the medical profession.

Dr. Charles S. Houston, an internist practicing in Exeter, New Hampshire, was the director of the assault on K2 in the First American Expedition (1938), having been a member of the British-American Himalayan Expedition that, in 1936, had reached the summit of Nanda Devi (25,600 feet), the highest mountain then climbed. On K2, although he and his fellow adventurers did not reach the top, they pushed their way to the foot of the summit pyramid, at a height of 26,000 feet before starting down. A way to the top had been found. A second expedition, in 1939, without Houston, also failed,

through misadventure, but such is the driving force inherent in mountaineers that a third attempt was made in 1953, with Dr. Houston in the lead. This too was unsuccessful, but under circumstances beyond control, when 8 men were trapped on the mountain for ten days near the summit in three small tents by a blizzard that made advance or retreat impossible. No one thought, during those ten terrible days, why they had come to such a perilous position, for their whole energies were focused on survival. The deepest springs of character were tapped. Dr. Houston, in an analysis of these "springs of character," has given a penetrating and cogent account and one cannot do better than quote his own words:

> The lack of oxygen at great altitudes may dull the mind and weaken the body, but there is an inner strength of spirit, a bigger power which emerges undiminished, even magnified, to bring a man through such an experience. We faced nature's wildest forces with our pitifully feeble tents and clothing as our only weapons, plus our inner determination. Perhaps it is this conquest, conquest of one's self through survival of such an ordeal, that brings a man back to frontiers again and again. It may be a storm at sea, the arctic cold, or the desert heat. It may be a frontier of the spirit or of the mind. By testing himself beyond endurance man learns to know himself. He endures and grows. Each generation passes the limits defined by its elders; the passage of the oceans, the reaching of the poles, flight, the four-minute mile, the theory of relativity, atomic fission. In a small way the conquest of a great peak is such a frontier.

The answer to the question "Why climb mountains?" has seldom been expressed, moreover, in a more fitting form than in Houston's words:

> The answer cannot be simple; it is compounded of such elements as the great beauty of clear cold air, of colors beyond the ordinary, of the lure of unknown regions beyond the rim of experience. The physical fitness, the pride of conquering a steep and difficult rock pitch, the thrill of danger — but danger controlled by skill — are also there. How can I phrase what seems to me the most important reason of all? It is the chance to be briefly free of the small concerns of our common lives, to strip off nonessentials, to come down to the core of life itself. Food, shelter, friends — these are the essentials, these plus faith and purpose and a deep and unrelenting determination. On great mountains all purpose is concentrated on the single job at hand, yet the summit is but a token of success, and the attempt is worthy in itself. It is for these reasons that we climb, and in climbing find something greater than accomplishment.

This "deep and unrelenting determination" has recently been expressed by another physician, Roger Gilbert Bannister, the first to run the faster-than-four-minute mile: "It's the ability to take more out of yourself than you've got." But he sees more in it than that, for running, he writes:

> . . . has taught me one thing: the need to make decisions. Sooner or later in sport we run up against situations which are too big for us to manage. . . . It shakes our roots with its confusing pattern of success and failure . . . Quick decisions are needed. As a result, sport leads to the most remarkable self-discovery of our limitations as well as our abilities.

Such "self-discovery" has come to many, in peace and war, but to none more deeply or clearly than to the physician mountaineers, from Paccard to Houston.

ANURIA FOLLOWING PHENYLBUTAZONE THERAPY

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IN recent years there has been an increased use of phenylbutazone (3,5-dioxo-1, 2-diphenyl-4-n-butyl pyrazolidine) as a general antiarthritic. Because of possibly indiscriminate administration and subsequent harmful effects, it is considered timely to review some of the more important toxic side reactions, and to include a case report of an undesirable sequela.

In a review of the literature, many complications and toxic reactions have been listed, including the following: granulocytopenia; thrombocytopenia; temporary and mild secondary anemia; hepatotoxicity and jaundice; Stevens–Johnson syndrome and other cutaneous manifestations; sensitivity reactions resembling polyarteritis nodosa; reactivation of peptic ulcer, with perforation and hemorrhage; retention of water, sodium and chloride, with consequent edema; hematuria; renal failure; and precipitation of uric acid stones.

Physiologic studies have revealed that phenylbutazone reduces the plasma urate level in both gouty and nongouty persons, but that this reduction is not associated with an increase in the excretion of uric acid in the urine. The means by which phenylbutazone lowers the plasma urate level is unknown. Two probable explanations have been proposed: the uric acid may be changed in chemical nature while in the body and excreted in an unrecognized form; and a new compound may be created whereby the urate is bound. It is suggested that it is thus removed from the "miscible pool" while it still remains in the body.

Steinbrocker and his associates‡ have described acute attacks of renal colic in 3 patients receiving phenylbutazone. In 2 of these cases the episodes recurred on readministration of phenylbutazone. In 1 case, analysis of the stone removed cystoscopically revealed it to be composed of uric acid crystals. In none of these cases had there been any pre-existing symptoms of renal colic. It was the impression of the authors that, in the susceptible persons, uric acid calculi are occasionally precipitated by phenylbutazone for as yet unknown reasons. It is the purpose of this report to alert the physician to the insidious development of renal calculi with such therapy, and to report a case in which the complication induced complete anuria.

CASE REPORT

W.M.H. (S.H. 95812), a 76-year-old man, was admitted to the hospital on August 19, 1954, with a chief complaint

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‡Steinbrocker, O., Neustadt, D. H., and Ehrlich, M. Butazolidin in treatment of gout. *M. Clin. North America* 611-623, 1954.

of anuria of 6 hours' duration, associated with discomfort in the suprapubic region. He had been under medical care for congestive heart failure, diabetes and generalized arthritis. He had been taking 15 units of protamine zinc insulin daily, as well as digitalis (0.9 gm.), and had received no mercurial diuretics during the preceding 3 weeks. Phenylbutazone had been taken for several weeks without medical supervision.

Except for the inability to void he had no complaints on admission. Physical examination revealed osteoarthritic changes in the joints of the hands and feet. Examination of the heart showed hypertrophy of the left ventricle, an apical rate of 72 and systolic murmurs at the apex and in the aortic areas. There were moist rales at the base of the right lung. The blood pressure was 110/70. No organs or masses were palpable in the abdomen, nor was there any tenderness. However, on the 2d hospital day, some tenderness developed in the left flank. There was no peripheral edema.

The urine had a specific gravity of 1.015, and the sediment contained 50 to 60 red cells per high-power field, with a moderate number of urates. Examination of the blood disclosed a hemoglobin of 11.5 gm. per 100 cc., and a white-cell count of 11,800, with 82 per cent neutrophils. The nonprotein nitrogen was 90 mg., and the blood uric acid 5.7 mg. per 100 cc.

Catheterization at the time of admission yielded 60 cc. of slightly cloudy urine, and a Foley catheter was left indwelling. There was no further urinary output during the next 24 hours. Cystoscopic examination showed the bladder to be empty and the mucosa to be inflamed throughout. There was mild prostatic hypertrophy. Both ureteral orifices appeared normal. A fine, orange-colored, sandy deposit characteristic of uric acid sand was noted on the bladder floor. (Analysis of all calculi removed demonstrated that they were composed of uric acid.) A No. 5F ureteral catheter passed up the right ureter to 20 cm., where impassable obstruction was encountered. On the left, a similar obstruction was noted 3 cm. from the orifice. A plain film of the abdomen revealed no radiopaque shadows resembling stones. Ureterograms confirmed the presence of bilateral ureteral blockage at the highest point of ascent of the catheters. An indwelling catheter was taped in place in the right ureter in the hope of promoting urinary drainage. This procedure had to be repeated twice before adequate urinary output was established from the right kidney. Calculi in the left ureter were impacted, and catheterization was impossible on this side on 3 attempts. The patient voided satisfactorily and was ready for discharge with the nonprotein nitrogen stabilized at 60 mg. per 100 cc. when he suddenly became dyspneic and cyanotic, and died.

Post-mortem examination revealed a bilateral hydronephrosis due to multiple uric acid ureteral and renal calculi. Recent acute anterior myocardial infarction was noted. Pulmonary embolization to the right lung, recent, in addition to the acute myocardial infarction, was stated to be the cause of death. There was also generalized arteriosclerosis, arteriolar nephrosclerosis, chronic passive congestion of the lungs, liver and spleen, benign prostatic hypertrophy and acute chronic pyelonephritis, bilateral.

Discussion

From this case it is evident that retention of water, sodium and chloride was undoubtedly a factor in the development of congestive heart failure. It is interesting to speculate whether, during the stage of oliguria resulting from this mechanism, uric acid crystals were precipitated. Steinbrocker et al. have stated that phenylbutazone should probably be withheld from patients in whom renal calculi are likely to develop. However, since it is known that the type of stone formed during phenylbutazone therapy is composed of uric acid crystals, it would be especially important to withhold this drug from patients in whom such a stone has previously formed. Because of the possibility of bilateral ureteral obstruction from calculi, these patients should be observed for oliguria as a forerunner of complete anuria. Any patient who becomes anuric in the course of phenylbutazone therapy should have the benefit of complete urologic investigation.

We are indebted to Norman Yosko, M.D., for permission to report this case.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41251

PRESENTATION OF CASE

A sixty-five-year-old carpenter entered the hospital because of respiratory difficulty and paralysis of all four limbs.

For about two years the patient had had a slight rhythmic tremor of the right thumb and fingers, which was present at rest and did not interfere with skilled manual work. About six weeks before admission he observed gradually increasing clumsiness of the right hand, so that he tended to drop objects, did not use a screw driver as well as before and began to miss with the hammer. The tremor was more severe, but there was no actual weakness during this period. Because of these symptoms, the patient received osteopathic treatment consisting of passive movements of the neck sixteen days before admission. On the next day he had aching pain in the posterior muscles of the neck aggravated by any neck movement. Over the subsequent days the neck pain became gradually worse. Five days before admission, he complained that his right hand "did not feel right," but did not describe the abnormality more fully. On that day, after a second osteopathic manipulation of the neck, the neck pain was more severe, and radiated into both shoulders and down both arms. On the following day, the patient found that he was unable to rock his small granddaughter on his knee, because of weakness, and at work the next day, he fell several times. On this day he experienced "pins-and-needles" sensations in both hands and feet. Two days before admission, he had difficulty in steering an automobile and in manipulating the foot pedals. On the next day he was unable to stand or to urinate, and was admitted to another hospital. Physical examination at that hospital disclosed marked weakness of the right arm and leg, with only slight weakness of the left limbs. There was slightly diminished sensitivity to pinprick in the right hand. Position and vibration senses were intact. Tendon reflexes were absent in the right arm, but normally active in the left, and present in the legs, the left being more active than the right. There was no abnormal plantar response. Roentgenograms of the cervical spine were normal. Films of the chest showed active bilateral apical pulmonary tuberculosis. Over the ensuing hours, he developed severe weakness of the left limbs. About twenty-four hours after entry, there was complete flaccid paralysis of all four limbs, and the tendon and plantar reflexes were unobtainable. Sensation was absent below the level of the ninth thoracic nerve root on the right and the tenth to eleventh thoracic nerve root on the left. Respiratory movements seemed weak. He was transferred to this hospital shortly afterward.

There was no history of exposure to toxic chemicals or other toxins or respiratory or other infectious diseases. The past and family histories were otherwise irrelevant.

Physical examination revealed a slender man who appeared acutely ill, but was alert and oriented. He complained of severe neck pain with any movement of the head or trunk. The general examination was not remarkable. On neurologic examination there was complete flaccid paralysis of the limbs. The anal sphincter was lax. Vision, fundi and ocular movements were normal. The pupils were 4 to 5 mm. in diameter and reacted promptly to light and on convergence. The palpebral fissures were somewhat narrow bilaterally. Corneal reflexes and sensation and movements of the face were normal. The gag reflex was not obtained, but there were good movements of the soft palate and tongue. The trapezius and sternocleidomastoid muscles on both sides were strong. Respiratory movements were weak. He was unable to cough. There were fasciculations in both arms. Deep and superficial reflexes were absent in the trunk and limbs. Sensory examination, made difficult by the patient's fatigability, showed diminished to absent perception of pinpricks and light touch below about the level of the fourth thoracic nerve root on the right and the sixth thoracic nerve root on the left. In addition there was hypalgesia and hypesthesia of both arms extending into the axillas. Sense of passive movement was absent at the elbows and knees. Vibration (C128 tuning fork) was felt at the ankles and wrists.

The temperature was 99°F., the pulse 64, and the respirations 14. The blood pressure was 130 systolic, 58 diastolic.

Lumbar puncture gave clear, colorless fluid under an initial pressure equivalent to 150 mm. of water. Jugular compression, digitally and with a pneumatic cuff, produced a rise equivalent to 250 to 300 mm. of water in ten seconds with a fall on release of compression to 150 mm. in ten to fifteen seconds. The fluid was clear and contained 3 lymphocytes per cubic millimeter and a total protein of 47 mg. per 100 cc. and a sugar of 100 mg. per 100 cc.; the Wassermann

reaction was negative. Routine blood and urine studies were within normal limits.

On the second hospital day, because of complete respiratory paralysis, the patient was put into a respirator, and a tracheotomy was performed. Streptomycin and penicillin were begun. ACTH was given intravenously but was discontinued the next day because of an episode of vomiting of bloody material. At this time, and on two occasions during the following week, he became suddenly cyanotic and unresponsive but responded well to tracheobronchial aspiration, with return of good color.

For several days, there was little change in the neurologic state except that more marked loss of vibration sense was noted, and the patient was unable to swallow. On examination on the eighth hospital day he continued to complain of pain on movement of the neck. There were bilateral ptosis of the eyelids, miosis and questionable anhidrosis of the face. Movements of the eyes, face and tongue were good. Flaccid quadriplegia persisted, with absence of deep reflexes. There was a minimal extension plantar reflex bilaterally. The sensory level was at the fourth to fifth cervical nerve root. The pulse ranged between 40 and 60; the systolic blood pressure fluctuated between 110 and 80 mm. of mercury. The temperature varied between 96 and 100°F. On the ninth hospital day the patient had another episode of cyanosis, associated with brief asystole, after which he never recovered consciousness and died twenty hours later.

Differential Diagnosis

Dr. John F. Sullivan*: A sixty-five-year-old carpenter entered the hospital because of respiratory difficulty and paralysis of all four limbs. For about two years the patient had had a slight rhythmic tremor of the right thumb and fingers, which was present at rest and did not interfere with skilled manual work. I do not believe that this was related to the present illness, for I cannot conceive of cervical-cord disease that would produce a rhythmic tremor and that would not produce either a motor or sensory deficit and would not interfere with skilled use of the extremity. This may have been an essential tremor. About six weeks before admission he observed gradually increasing clumsiness of the right hand and increasing severity of the tremor. I presume that there was absence of any subjective sensory disturbance. It is possible that at this time the patient's difficulty arose from posterior-column disturbance on the right. The fact that the tremor was worsened could have been due, therefore, to the addition of a sensory ataxia.

The patient received osteopathic treatment, after which the neck pain became gradually worse. I call attention to the fact that although he had increasing pain over the next eleven days, there was no note made of increasing disability. It would suggest to me that the osteopathic manipulation may have resulted in some damage to the neck that did not involve the nervous system at this time. For example, with an acute necrosis or demyelinative myelitis causing acute pain, one would expect evidence of progression of the process. The ACTH, I presume, was given with the thought that the patient's illness may have been an acute demyelinative process. I wonder, in view of subsequent events, whether the severe neck pain that radiated into both shoulders and down both arms after the second osteopathic manipulation was medullary pain — that is, pain of intraspinal rather than radicular origin. Such pain is often of burning or distending character. On the other hand, at the age of sixty-five, the patient may well have had cervical spondylosis. Often in this condition there is root-sleeve fibrosis, with which the nerve roots are tied down, lack their normal mobility and are thus far more susceptible to trauma. The osteopathic manipulation may have been sufficient to have initiated the pain by traumatizing the nerve roots.

The increasing weakness leading to falls, the pins-and-needles sensation in both hands and feet, the difficulty in steering an automobile and in manipulating the foot pedals and the inability to stand or to urinate are evidence of the rapid evolution in a period of three days of an affection involving all four limbs and bladder function. This was confirmed by physical examination, which revealed more marked weakness of the right arm and leg and slightly diminished sensitivity to pinprick in the right hand. In view of the above-mentioned increasing clumsiness of the right hand without objective sensory disturbance, I should wonder about this observation that the position and vibratory senses were intact. The absence of tendon reflexes in the right arm suggests either anterior-root involvement or an affection within the spinal cord affecting anterior horns over 3 or 4 segments. I am concerned about the finding of diminished reflexes in the right leg, but cannot explain this at the moment. Twenty-four hours before entry, there was complete flaccid paralysis of all four limbs. The absence of tendon reflexes is probably consistent with the rapid development of quadriplegia and probably represented a state of spinal shock rather than widespread root or peripheral-nerve affection. The information that there was no history of respiratory or other infectious diseases probably was included with the thought that this patient might have an acute demyelinative process or transverse myelitis, often preceded by an ill defined infectious process. The normal corneal reflexes and sensation and movement of the face are somewhat surprising since the process appears to have extended into cervical segments, and I would anticipate involvement of the descending spinal tract of the fifth nerve, with diminished pain sensibility in the upper face and diminished corneal reflexes. The complete respiratory paralysis also indicates extension to the fourth cervical segments. The

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fasciculations in both arms would suggest intrinsic cord disease with involvement of the anterior horns of gray matter bilaterally.

It is difficult to interpret the rise in spinal-fluid pressure to 250 to 300 mm. of water in ten seconds with a fall on release of compression to 150 mm. in ten to fifteen seconds. A rise of only 100 to 150 mm. is not very great. If it had risen to 400 or 500 mm., with an equally rapid fall, I should be satisfied that there was no dynamic block. The figures, as given, may signify a partial block. The spinal fluid was normal, and the total protein of 47 mg. per 100 cc. does not suggest a dynamic block.

The episodes of cyanosis that responded to tracheobronchial aspiration, of course, resulted from tracheobronchial plugging because of inability to clear the respiratory passages. The bilateral ptosis of the eyelids, miosis and questionable anhidrosis of the face indicate bilateral Horner's syndrome, and the inability to swallow indicates that the process had extended into the medulla. I suspect that the episode of cyanosis on the ninth hospital day from which the patient never recovered was sufficiently prolonged to have caused anoxic changes in the brain and death on that basis.

In discussion, I should like to go back not to the beginning of the history but to the point of the manipulations of the patient's neck, for I believe that there are two factors in this case. It is more than coincidence that the first discomfort the patient suffered followed this manipulation, that it worsened after the second manipulation and that then the evidence of severe damage to the cervical cord developed quite rapidly. One possibility, of course, is an acute protrusion of an intervertebral disk. Against this is the absence of block on manometric examination. I suspect rather than this that the patient probably had spondylosis with protrusion of the annulus fibrosus and that manipulation resulted in interference with the blood supply to the cord, with edema and infarction. This need not result in instantaneous quadriparesis, for there may be progression over a few days to a few weeks. I refer to Case 6 in Sir Charles Symonds's article,* in which, after manipulation of the head during tonsillectomy, a patient showed progression of cord damage over a period of about three weeks. However, I am quite concerned about the fact that this process in the patient under discussion seemed to extend in a vertical direction and appeared to progress up the cord to the medulla. Is it possible that the manipulations had nothing to do with this and that the patient had an acute myelitis, which often occurs without any apparent antecedent disorder? This includes a variety of pathologic processes — including acute parenchymatous myelitis with or without perivascular infiltration and hemorrhage, and an acute demyelinative process. The onset and course of these entities varies widely from acute and catastrophic to subacute over a week or two. It would be unusual, however, for such a process to have produced focal damage to the cord, which remained essentially unchanged for a period of five weeks, caused severe pain for ten days during which there was no progression of symptoms and then suddenly after the second manipulation resulted in the rapid development of the symptoms. That does not quite seem to me to be the course that one would expect with a myelitis. The spinal-fluid findings are also somewhat against that. It is true that the spinal fluid in some of these cases may be normal but for the most part there is an elevation of lymphocytes if only of 8 to 30 cells per cubic millimeter.

Thus far the case has been discussed largely from the point at which the patient underwent the first manipulations. Was the original disturbance with increasing clumsiness of the right hand but without weakness or subjective sensory disturbance six weeks before admission evidence of cervical-disk disease, which we have termed spondylosis? When the neck is not subject to manipulation, as in this case, the development of the neurologic deficit due to spondylosis is usually chronic and very gradual. Symptoms ordinarily are due either to protrusion of the nucleus pulposus, which then becomes calcified with the formation of what have been called osteophytes, or to collapse of the disk and protrusion of the annulus fibrosus diffusely across the anterior portion of the cord. If the protrusion is lateral, encroaching upon the intervertebral foramen, a dull, aching pain in the dermatome involved usually results. This was absent here. If the symptoms are caused by diffuse protrusion of the annulus, a variety of clinical syndromes develop that may simulate syringomyelia, motor-system disease, combined system disease and others. The absence of pain bothers me but does not cause me to discard this notion. However, it would seem to be unusual for spondylosis to present as involvement of the posterior column on one side. If I could be sure that examination at that time would have shown only posterior-column affection, I should be inclined to believe that the patient had pre-existing intrinsic disease of the cord developing rather gradually until the manipulation of the neck. The final impression, therefore, is that the patient had cervical spondylosis with infarction and necrosis of the cervical cord extending into the medulla, and intramedullary cord disease, the nature of which cannot be determined from the protocol.

Clinical Diagnoses

Transverse myelopathy, third and fourth cervical level.
?Arterial thrombosis.

Dr. John F. Sullivan's Diagnoses

Spondylosis of cervical cord, with infarction and necrosis extending to medulla.

*Symonds, C. Interrelation of trauma and cervical spondylosis in compression of cervical cord. *Lancet* 1:451-454, 1953.

Pre-existing intramedullary cord disease, type undetermined.

Anatomical Diagnoses

Glioblastoma multiforme, cervical spinal cord.
Intramedullary hemorrhage, medulla oblongata and entire spinal cord.
Pulmonary tuberculosis, active, right.
Bronchopneumonia.

Pathological Discussion

Dr. Edgar B. Taft: At autopsy the most important findings were in the central nervous system. One incidental finding was that the patient had tuberculosis that was moderately active and not inactive as the radiologist thought. Many tubercle bacilli and considerable granulation tissue in tubercles and in some of the lesions in the right apex were present. The other finding, which might well have been expected, was a moderately severe bronchopneumonia and rather marked pulmonary congestion and edema.

Dr. Edward P. Richardson, Jr.: We are all most grateful to Dr. Sullivan for his interesting discussion of an extremely difficult case. As it turned out, there was no description of the appearance of the cervical spine at the time of the autopsy. Attention was focused on the spinal cord because it was the site of major disease. There were no abnormalities in the brain, and nothing was found to account for the tremor, which had existed for some years before admission and was interpreted by various observers as Parkinsonian in nature.

On external examination the cord was slightly and diffusely enlarged in diameter in the cervical and upper thoracic regions. On section there was hemorrhage within the cord extending from the uppermost cervical region to approximately the first lumbar segment. The hemorrhage was most extensive at the level of the seventh to eighth cervical segments, where it occupied almost the entire substance of the cord. At higher levels, it involved the right half and tapered gradually as it approached the medulla. In the thoracic region the hemorrhagic area was for the most part in the center of the cord, and gradually diminished in extent toward the lumbar segments. Microscopically, surrounding the collection of extravasated blood at all levels there was a zone of variable width in which the cord tissue was necrotic, and was the site of an active cellular response consisting of increase in the number of macrophages and enlargement of astrocytes. This lesion could be followed upward into the medulla oblongata, where it occupied the right tegmental region as high as the lower end of the fourth ventricle.

At the seventh cervical level in the right side of the cord, and in the anterior portion in the left, peripheral to the central hemorrhagic and necrotic area, there was a densely cellular, undifferentiated infiltrating neoplasm composed of fusiform cells of rather variable size. The stroma of the tumor contained numerous glia fibrils, but no reticulum fibers except in the vascular adventitia. Multinucleated cells and mitoses were frequent. In the region of the anterior horns a few motor-nerve cells remained, entirely surrounded and engulfed by tumor tissue. The tumor was restricted to this level of the cord, although above and below it were the hemorrhage and necrosis already noted.

We have to classify this tumor as glioblastoma multiforme, a malignant tumor of astrocytes. The interpretation of the other changes is difficult. Obviously, the tumor was associated with a major degree of hemorrhage into the cord, and the hemorrhage extended upward and downward. Much of the necrosis must have been due to the presence of the hemorrhage. We wondered in addition if the presence of the tumor, with the swelling of the cord occasioned by it, might have interfered with the blood supply of the cord and thus have resulted in infarction of the cord. What part the neck manipulations may have played in this is a question that we must leave open. We could also wonder whether the hemorrhage might have been thereby made more extensive, but we have no definite proof. Much of the hemorrhage was not of recent appearance, but, in view of the active cellular response to it at all levels, must have been there for some days at least, although not for weeks.

Dr. Raymond D. Adams: I think the pathological findings were a complete surprise to everyone. I do not believe a single person who had anything to do with the patient on the ward thought of tumor. I saw the patient a few hours before he died for the first time and was given the same history as was presented to Dr. Sullivan. We thought the best interpretation of all these findings was that the patient had had paralysis agitans of mild degree, with the usual tremor and slowness of movement, and then a superimposed process — an acute myelitis or vascular lesion of the cervical cord. None of us thought of explaining both the six-week history of pain and rapidly developing motor paralysis in the last illness as manifestations of a rapidly growing intramedullary tumor. Perhaps we should have considered this possibility, but the clinical picture was bizarre; I doubt that we could make the diagnosis if we were confronted with a similar case again. We discussed the possibility that the manipulation may have induced hemorrhage into the spinal cord or have led to a vascular occlusion of some of the branches of the vertebral artery.

CASE 41252

Presentation of Case

First admission. A fifty-year-old man entered the hospital because of severe headache.

Twelve days before admission he noticed a severe

left frontotemporal headache and inability to see objects on the right. The headache improved gradually, but the visual disturbance remained. Two days before admission he had several seizures characterized by generalized spasticity with outstretched arms.

The patient had previously been in good general health. He had, however, experienced two episodes of "cramps" in the right upper abdomen. The first occurred fourteen years previously and lasted for two weeks; a Graham test done at that time showed "biliary-tract spasm." The second similar episode was thirteen years later. About six months before admission the patient noticed dark urine, which was found to contain bile. Gallstones were never demonstrated. There was no history of jaundice, itching or anemia.

Physical examination revealed a well developed and well nourished man. There was right homonymous hemianopsia and slight right facial weakness. The tendon reflexes were more active on the right. The plantar reflexes were normal. There was moderate speech difficulty. The only other positive finding was enlargement of the spleen; its edge was felt 1 fingerbreadth below the costal margin.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 170 systolic, 90 diastolic.

The urine had a specific gravity of 1.018 and gave + tests for albumin and bile; the sediment contained occasional red and white cells per high-power field. Subsequent examinations revealed no bile. Urinary urobilinogen was 3 Ehrlich units in a two-hour specimen. Examination of the blood showed that the hemoglobin varied from 14.4 gm. to 12.8 gm. per 100 cc., and the white-cell counts from 3600 to 8600, with normal differentials. The reticulocyte count was 1.5 per cent. The total protein was 6.7 gm. with an albumin-globulin ratio of 1.5, the bilirubin 0.9 mg. direct and 1.3 mg. total, the fasting blood sugar 218 mg., and the alkaline phosphatase 17 units per 100 cc. Cephalin flocculation was negative. The prothrombin time was 21 seconds (normal, 17 seconds). The bromsulfalein test showed 30 per cent retention of the dye. The bleeding time, clotting time and clot retraction were normal. The blood Hinton test was negative. The guaiac test on the stool was negative. The cerebrospinal fluid was normal. X-ray examinations of the skull, chest and abdomen were negative except for enlargement of the spleen. A gastrointestinal series revealed varices in the lower end of the esophagus, prominent gastric rugae and a diverticulum in the second portion of the duodenum. An intravenous pyelogram was normal. A Graham test showed poor concentration of the dye; areas of calcification were present in the right upper abdomen.

The neurologic signs and symptoms improved slowly. Two weeks after admission the serum bilirubin increased to 5.8 mg. direct and 8.4 mg. total per 100 cc., and the next day, a peritoneoscopy was performed. A biopsy specimen of liver revealed acute and chronic cholangitis, but no cirrhosis. The serum bilirubin fell four days postoperatively to 1.7 mg. per 100 cc. total. On the twenty-sixth hospital day the abdomen was explored. The liver appeared normal. The gall bladder was surrounded by adhesions. The common bile duct revealed no evidence of obstruction. It contained muddy material but no calculi. In the course of cholecystectomy a friable tumor was discovered in the gall bladder. Pathological examination showed adenocarcinoma. The spleen was noticed to be moderately enlarged, but palpation of the splenic and portal veins and of other abdominal organs revealed no abnormality. A manometric reading taken in a large omental vein was 32 cm. of water. A biopsy specimen of liver showed mild cellular infiltration, but no evidence of cirrhosis. The patient was discharged three weeks after the operation with a T tube in place.

Final admission (four and a half years later). Two cholangiograms taken five and eleven months after the cholecystectomy revealed considerable dilatation of the common duct and its biliary radicles with multiple nonopaque shadows in the common duct. Prompt flow into the duodenum was readily demonstrated. The T tube was removed eleven months after the operation. The patient was followed periodically in the tumor clinic. He was asymptomatic, and the physical findings were unchanged except that the spleen seemed to increase in size slowly. Three and a half years after the operation, the patient vomited some bright-red blood and noticed tarry stools for a few days. A gastrointestinal series done then revealed large esophageal varices, coarse gastric rugae and in addition a deformed duodenal cap. The patient continued to be well otherwise until nineteen days before admission, when he suffered a shaking chill followed by high fever with a temperature of 105°F. and accompanied by pain and burning on urination. He was treated with orange capsules by his physician, and the temperature returned to normal in four days. Ten days before admission he vomited a glassful of clotted blood and noticed a tarry stool. Three days later, he had diarrhea and vomited another quart of blood. There was no jaundice or abdominal pain.

Physical examination revealed that the patient was weak and very pale. The liver was palpable 2 fingerbreadths and the spleen 4 fingerbreadths below the costal margins. Rectal examination revealed an enlarged prostate and external hemorrhoids.

The temperature was 99.2°F., the pulse 120, and the respirations 24. The blood pressure was 120 systolic, 80 diastolic.

The urine was acid, negative for albumin and bile and gave an orange reaction for sugar; the sediment was loaded with white cells. Examination of the blood revealed that the hemoglobin was initially 7 gm. but rose to 11.5 gm. per 100 cc. after repeated transfusions, and the white-cell count was 13,500. The sodium was 127 milliequiv., the potassium 4

milliequiv., the chloride 98 milliequiv., and the carbon dioxide 25 milliequiv. per liter; the fasting blood sugar was 280 mg., the nonprotein nitrogen 25 mg., the alkaline phosphatase 9.1 units, and the bilirubin 3.1 mg. per 100 cc. The prothrombin time was 15 seconds (normal, 13 seconds), and cephalin flocculation was negative. The bromsulfalein test showed 32 per cent retention of the dye. An x-ray film of the chest revealed a slight increase of bronchovascular markings. A gastrointestinal series again revealed varices and large gastric folds (Fig. 1). There was a suggestion of abdominal fluid. The urine culture grew out *Staphylococcus albus.*

FIGURE 1. *Right Anterior Oblique View from Examination of the Upper Gastrointestinal Tract, Showing Large Varices of the Lower Esophagus and Gastric Fundus.*

On the sixth hospital day the patient had another episode of massive hematemesis. A transthoracic ligation of the esophageal varices was performed the next day. Three days postoperatively the nonprotein nitrogen increased to 120 mg. per 100 cc., and the potassium to 5.3 milliequiv. per liter. The temperature rose to 105°F., and the patient died on the ninth hospital day. Treatment included penicillin, streptomycin and many transfusions.

DIFFERENTIAL DIAGNOSIS

DR. JACOB LERMAN*: I think I can dismiss the initial episode that necessitated the first admission as one of vascular thrombosis, which localized in the left hemisphere with partial hemiplegia and involved the left optic nerve. This may or may not have been related to the final illness. I know that there was something wrong in the right upper quadrant in the region of the liver for about eighteen years before death. The patient had had two episodes of pain and then evidence of jaundice later, with bile in the urine on several occasions and laboratory evidence of liver damage.

I think at this point I had better see the x-ray films.

DR. C. C. WANG: The films of the chest taken during the first admission show essentially clear lungs and a heart that is not unusual. The films taken during the last admission, approximately five years later, demonstrate considerable elevation of both leaves of the diaphragm and some increased prominence of the pulmonary markings. The gastrointestinal series reveal a tremendous increase in the size of the mucosal folds in the proximal half of the stomach (Fig. 1); spot films of the lower end of the esophagus show widening and tortuosity of the esophageal folds, which have the typical appearance of esophageal varices. In the film of the abdomen taken during the first admission there is considerable enlargement of the splenic shadow. Intravenous urograms show that the left kidney is displaced inferiorly, but the collecting systems on both sides appear fairly normal. A film of the abdomen, five years later, shows considerable increase in the size of the spleen. There is some haziness of the abdominal organs, suggesting the presence of ascites. A gastrointestinal series done on the last admission shows considerable increase in the size of the esophageal varices; there are multiple radiolucent defects in the gastric fundus extending to the proximal half of the stomach, which I would interpret as gastric varices. There is no significant deformity of the duodenal cap nor widening of the duodenal loop. There is a diverticulum in the second portion of the duodenum. The cholangiogram shows multiple radiolucent defects in the slightly dilated common duct that are probably radiolucent stones.

DR. LERMAN: Yet at operation no stones were visible! When was this x-ray film taken in relation to the first operation?

DR. WANG: That was after the operation. In interpreting the Graham test, I can add nothing that is not stated in the protocol.

DR. LERMAN: Obviously, the surgeon was trying to determine the cause for the portal hypertension when he palpated the various venous systems. He ruled out portal-vein thrombosis and tumor masses that may have obstructed the portal vein. It is conceivable that he could miss intrahepatic thrombosis or a tumor mass within the liver parenchyma obstructing the portal system. If such a mass were present, it would also have obstructed the biliary tree, and the patient would have been severely jaundiced.

I might begin with the conditions that obviously were present. The patient, at the time of the final admission, undoubtedly had acute pyelonephritis as evidenced by the symptoms, the findings in the urine and the urinary culture. In addition he had diabetes and some sort of liver disease. This raises the question of hemochromatosis. The absence of pigmentation and of any iron studies on the blood argues

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strongly against this diagnosis. Moreover, the cirrhosis of hemochromatosis is usually mild, and there is seldom much jaundice or evidence of collateral circulation; in this patient there was a great deal of portal hypertension and intermittent jaundice. I am inclined to rule out hemochromatosis.

Another point worth discussing is the nature of the kidney findings. The renal function seemed to be fairly good as evidenced by the fact that during the episodes of bleeding the nonprotein nitrogen remained normal. However, on the final admission, azotemia developed rapidly. Azotemia, in the presence of long-standing diabetes, always raises the question of underlying kidney damage, such as Kimmelstiel–Wilson disease or nephrosclerosis. I can only mention it without going any farther.

He had considerable evidence of portal hypertension, which developed slowly. It was first noticed during the first admission, when the spleen was enlarged and an increased pressure in the portal vein was found at operation. The continuing enlargement of the spleen, development of varices and bleeding, and increasing size of the liver all point to portal cirrhosis. Yet the biopsy on the first admission showed little or no evidence of cirrhosis. I must assume that this was a progressive development starting with portal hypertension and circumscribed fibrosis within the liver, and gradually becoming a full-blown cirrhosis.

There was also evidence of intermittent biliary obstruction, which began some eighteen years before the first admission. At operation there was evidence of cholangitis; later, there was progressive liver damage. In addition the high alkaline phosphatase and negative tests for hepatocellular function — such as the prothrombin time and the cephalin flocculation — point to obstructive biliary cirrhosis as part of the liver disease. I believe, therefore, that the patient had ordinary portal cirrhosis with portal hypertension and also obstructive biliary cirrhosis.

The question of a malignant process must be disposed of. He had a gall-bladder tumor removed four and a half years before death. I thought that the x-ray films might reveal that the shadows mentioned were due to metastases, but as Dr. Wang indicated, these were characteristic of gallstones and not of lymph nodes. Certainly, if there were metastases from the gall bladder, in a period of four and a half years, there would have been much more gross evidence of it by physical examination. It is hardly likely that a patient would live this long with metastases from a gall bladder without complete obstructive jaundice. I may, therefore, rule out metastases from the gall bladder.

Another source of malignancy is the pancreas. The patient had the condition too long without causing complete obstruction. The jaundice was never fixed, but was fluctuating. It would seem unlikely that there would not have been more evidence by physical examination of carcinoma of the pancreas after four and a half years of obstruction.

In the presence of cirrhosis of fairly long standing one has to raise the question of primary hepatoma. I searched the protocol for some clue to the presence of primary hepatoma, but I could not find an unusual episode to indicate the development of a tumor during the course of the disease. Death apparently was due to bleeding. One can only mention this and rule it out.

I am left with the diagnosis of portal cirrhosis combined with biliary cirrhosis and acute pyelonephritis.

Dr. A. B. Field: Do you think amyloid disease over a long period of time can produce this picture with portal obstruction and varices and perhaps a renal lesion?

Dr. Lerman: I had amyloidosis down to discuss, but was hesitant because I could not find enough evidence in the protocol to talk about it. The patient had long-standing cholangitis, which was enough to account for the liver damage. I do not know whether there was evidence of infection elsewhere. One might postulate primary amyloidosis in his case; I do not see how one could argue for secondary amyloidosis.

Dr. Benjamin Castleman: Dr. Jones, have you any comment? I do not know whether you have seen this patient or not.

Dr. Chester M. Jones: No, I did not. Dr. Lerman mentioned that he had not considered hemochromatosis. I am sure if he had, the biopsy would have been the most certain way of proving hemochromatosis so it is probably fair to throw that suggestion out. The diabetes could have been an independent condition, but it does suggest the possibility of the involvement of the pancreas by some process so that I am sure his suggestion that pancreatic disease had to be thought of was valid. Apparently, the finding of a high blood sugar was incidental, and the patient had no symptoms of diabetes.

I am still wondering about the validity of an observation made during an exploration that there was no suggestion of thrombosis of the portal venous system on the basis of palpation. The two liver biopsies did not show fibrosis; yet he did have portal hypertension at the time of operation. This still makes it possible that there was an extrahepatic block that was responsible for the portal hypertension and early development of varices. The biopsy may have failed to show a great deal of fibrosis in the liver, but the surgical biopsy presumably should have shown something besides evidence of cholangitis, which I think is what was originally described. There was not enough fibrosis of the liver to account for varix formation with any degree of certainty. I am sure that one can get an unusual point of venous obstruction that cannot always be palpated.

Dr. Alfred Kranes: I too am troubled, like Dr. Jones, by the presence of portal hypertension without any hepatic fibrosis at the first operation. This suggests extrahepatic portal obstruction.

Dr. Jones: If the patient had not been so ill when he came in at the time of the second admission, this was an ideal case for injection of the spleen with

dye to show the entire venous circuit in order to tell whether there was intrahepatic or extrahepatic block in the portal system. I suppose he was so ill it was not desirable to do that. If he had not had such a major hemorrhage, it might have been a very helpful maneuver.

DR. EDWARD B. BENEDICT: The liver at the time of the first admission was red, granular and yellowish; I think he had a definite cirrhosis then. My diagnosis was acute toxic cirrhosis in spite of the biopsy. I do not understand why twelve days later the surgeons said that at laparotomy the liver appeared normal; it certainly was not normal at peritoneoscopy.

DR. JONES: Were they gross nodules that could be rolled under the fingers?

DR. BENEDICT: No.

DR. JONES: Again and again one will see at operation a finely granular, firm liver, which can be the result of biliary cirrhosis or early cirrhosis of another type.

DR. BENEDICT: It was a very abnormal-appearing liver to me.

DR. LERMAN: Dr. Jones, I was depending a great deal on the skill of the surgeon in palpating the portal vein.

DR. JONES: I should too, but the surgeon cannot always demonstrate a condition he may suspect.

CLINICAL DIAGNOSES

Esophageal varices.
Cirrhosis of liver.
Uremia.

DR. JACOB LERMAN'S DIAGNOSES

Portal and biliary cirrhosis.
Acute pyelonephritis.
Diabetes mellitus.

ANATOMICAL DIAGNOSES

Cavernomatous change in region of portal vein (with portal hypertension).
Esophageal varices with massive hemorrhage.
Superior mesenteric phlebothrombosis extending into portal vein, recent.
Splenomegaly.
Choledochitis, chronic, with choledocholithiasis.
Prostatic abscesses.
Pyelonephritis, acute.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At the time of autopsy it was obvious that the patient died of massive hemorrhage. The stomach was full of blood, and there were, as expected, esophageal varices. Another factor, which may not have contributed to the death but certainly did to the illness in the last admission, was the infection of the genitourinary tract. There were a number of prostatic abscesses and a pyelonephritis secondary to that which apparently accounted for the renal symptoms and impairment. The spleen was very large, weighing 1300 gm. The splenic vein was perfectly normal, but in the superior mesenteric vein, just proximal to the portal vein, was a recent thrombus that extended to the portal vein. This thrombus was definitely recent and was therefore not a cause of the long-standing portal hypertension. The liver was quite smooth and red, and as evidence of severe portal hypertension, there was marked dilatation of the portal-vein radicles. The common bile duct was markedly dilated and thickened and did contain stones — a definite cholangitis. At the hilus of the liver marked varicosities were found throughout the region of the portal vein. This condition, which is sometimes called a cavernomatous transformation of the portal vein, is believed to be due to actual thrombosis of the portal vein with recanalization. Whipple,* in his paper on portal hypertension, discusses the cavernomatous transformation of the portal vein in detail, and states that the pathogenesis is probably a variable one: either a thrombosis with a recanalization, a congenital malformation or a true tumor such as a hemangioma. He stated that Pick believed that this was really an angioma. I personally would favor recanalized thrombosis.

DR. WALTER BAUER: Are you not ordinarily able to decide whether there is recanalization?

DR. CASTLEMAN: It is difficult to decide at this late stage in the disease. In children it is believed that one of the causes of esophageal varices is an extension of the normal closure of the umbilical vein into the left portal vein, gradually occluding it and later involving the right portal vein. It is possible that this same etiology is applicable in the adult cases, the involvement being less severe and taking a longer time to cause symptoms. In those cases one would not expect cirrhosis, and there was no cirrhosis in the case under discussion. Near the surface there was some fibrosis — not a real cirrhosis.

The other possibility that I considered is whether the long-standing chronic cholangitis, which this patient certainly had, could have in some way sufficiently obstructed the portal veins within the liver to produce this secondary change; however, there was no biliary cirrhosis. He recovered from the obstruction when the gall bladder was removed.

The tumor in the gall bladder was a friable, polypoid mass, which five years ago we called an adenocarcinoma. In looking at the slides now I should be more inclined to call it an adenomatous polyp. There is very little atypicality of cells. Some pathologists might call it a low-grade adenocarcinoma; apparently, we did five years ago. I may be biased by the fact that he had been cured of the disease, but today I would not call it malignant.

A PHYSICIAN: What did you find in the pancreas?

DR. CASTLEMAN: It was normal. The lungs showed some edema.

*Whipple, A. O. Problem of portal hypertension in relation to hepatosplenopathies. *Ann. Surg.* **122**:449-475, 1945.

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

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"NARROW IS THE WAY"

A NEWSPAPER columnist reviewing poliomyelitis developments during the spring of 1955 comes to the conclusion that "there are those who have had great misgivings ever since April 12 about the dramatic buildup, the theatrical suspense and the spectacular publicity with which the Salk vaccine was proclaimed."[1] Among those with misgivings are many physicians and scientists. Although they remain satisfied with the scientific way in which the experiment of the past year was conducted — and this depended primarily on the use of a code that could not be cracked, no matter how great the pressure — they are disturbed at the dramatic way in which the denouement was announced, as though the occasion were a Hollywood *première* presented to an admiring public. The event itself was ushered in with skillful suspense, scientific data being presented before a national radio and television audience and newspaper reporters, whose presence seemed to be in greater demand than that of Nobel prize winners.

The result has been to show once again that the business technics so successful commercially are not the ones that should be used in the field of therapeutic or preventive medicine. Scientific ventures with life-and-death import may have weighty commercial aspects. The ventures themselves should not be commercialized.

None of these strictures are intended to deprecate the fine scientific work of the principals involved nor of the contribution of the National Foundation for Infantile Paralysis itself. As the same columnist goes on to say: "The foundation has done great and necessary things in its field. This is dependent, as all know, upon voluntary popular subscription." However, as he points out, the promotion and publicity that are effective in fund raising (and that are so distasteful to many members of the medical world), "should have been kept carefully distinct from the publication of medical news."[1] Physicians will agree. They too, as well as foundation administrators, have their responsibilities in these matters; and it is for physicians to resist the danger of being maneuvered into unscientific positions that put their prestige in jeopardy.

Nor should a political whipping boy be set up to obscure the deeper issue that has been laid bare by an initial lack of organization in controlling the distribution of the vaccine and the vaccine's failure to provide immediately complete, permanent and safe protection against poliomyelitis in all cases; this deeper issue is the National Foundation's "circus"[2] announcement of the apparent efficacy of the product. It is the more sobering to realize that if the vaccine had been an instantaneous success anyone who made very much of the objections that seem so plain today would have been laughed down or gently ignored; and yet the criticisms that have been leveled against the method of announcing the results would still have been valid.

In the final analysis it is physicians who must assume some of the responsibility for allowing themselves to be drafted by methods of the modern impresario into a scientific version of grand opera. How far they have risked delivering themselves into bondage is best demonstrated by the blanket castigation given by Mr. O'Connor of attempts to assume rightful responsibilities by other than Foundation-sponsored scientists. "So long as the Salk vaccine and its research were in the hands of the National Foundation, you had some intelligence, intellectual integrity and total courage," he asserted, "—and you had no politics whatsoever." Such an impertinence speaks worlds in favor of keeping scientific programs under the control of scientists from beginning to end.

References

1. Lippmann, W. Officials went off half-cocked. *Boston Morning Globe* (Syndicated column). May 11, 1955.
2. *Newsweek*. May 30, 1955.

DIRECTOR OF MEDICAL EDUCATION

In the naming of Chester Scott Keefer as director of Boston University School of Medicine, the trustees of the University have assured the school of a continuance of the progressive program to which the retiring dean, Dr. James M. Faulkner, has made such valuable contributions.

Dr. Keefer, for fifteen years Wade Professor of Medicine at the University and physician-in-chief of clinical research in preventive medicine at the Massachusetts Memorial Hospitals, has become one of Boston's distinguished physicians and citizens. Not only has he been instrumental in bringing the medical school to the fore in teaching and research; his own career in public service has been outstanding, first as chairman of the National Research Council's committee on chemotherapeutics during World War II, and for the last two years as special assistant on health and medical affairs to the Secretary of Health, Education and Welfare. Like so many eminent Boston physicians, Dr. Keefer has served time on the editorial board of the *Journal,* from 1941 to 1947, an experience that must have played no small part in shaping his character and fitting him for the positions that he has later come to occupy.

Born in Altoona, Pennsylvania, in 1897, Dr. Keefer received his B.S. and M.S. degrees from Bucknell University in 1918 and 1922, and graduated in medicine from Johns Hopkins University in 1922. Prior to joining the Boston University faculty in 1940 he had taught at Johns Hopkins, the University of Chicago and Peiping Union Medical College. He has also served for ten years on the faculty of Harvard Medical School.

Dr. Keefer's new appointment, new also in the history of Boston University, will combine the administrative functions of dean of the medical school with those of co-ordinating the school's educational program with the services of the Massachusetts Memorial Hospitals. This is a step, according to President Case's announcement, in the development of a Boston University Medical Center, which Dr. Keefer will eventually direct.

WORLD HEALTH ORGANIZATION — SIX YEAR SUMMARY

Dr. M. G. Candau, director-general of the World Health Organization, submitted to the Eighth World Health Assembly meeting in Mexico City this spring his annual report for 1954, marking the completion of six years of existence for the organization.

During the year WHO participated in 329 major health projects in 75 countries, pursuing for 1954's essential aim the strengthening of the structure of public-health activities in the various member states in place of short-term health campaigns.

The idea of international co-operation is growing among the member states, Dr. Candau believes, as evidenced by an increasing willingness to accept joint action in attacking mutual problems. Among the joint actions that have been thus undertaken have been the Inter-American Center of Biostatistics in Chile, the Regional College of Nursing in Egypt and an advanced course for waterworks engineers in Europe. Most prominent among such co-operative ventures have been international efforts in disease control, such as the agreement on a five-year plan of malaria eradication in all the American countries, reached at the fourteenth Pan-American Sanitary Conference at Santiago.

Tuberculosis control was continued in 28 countries. This consisted of 22 projects in mass BCG vaccination in addition to 18 concerned with instruction. During the year some 32,000,000 persons were tuberculin tested and 11,000,000 vaccinated. As previously noted, WHO assisted in field programs directed against treponemal and venereal infections in 20 countries. Other activities in the fight against disease included excursions into the field of veterinary public health, work on the diagnosis and control of viral infections and projects on the control of trachoma, diphtheria, typhoid fever, onchocerciasis, leprosy, plague, cholera, yellow fever, bilharziasis, relapsing fever and other afflictions.

A program for the study of poliomyelitis has been developed, and the research conducted in several countries on poliomyelitis vaccine has been scrutinized. It is believed, according to the report, that "prospects for eventual success are good" — a laudably conservative statement.

Other divisions of the report take up health services in the field, activities in training and education, and the financial position of the agency. Health services in the field have been undertaken in such separated areas of the global surface as Africa, Southeast Asia, Europe, the Eastern Mediterranean region,

the Western Pacific area and the Americas, where the Pan-American Sanitary Bureau, WHO's Regional Office for the Americas, assisted 20 countries with 58 different health schemes.

Dr. Candau, in the introduction to his report, foresightedly raised the most important question of all. This concerns the assessment that must be made of the far-reaching effects on health of new forces and new agents that have come into existence in a relatively short time. All of these, ranging from the creation of atomic energy with its problems of air, soil and water pollution and the disposal of its wastes to the wholesale destruction of insects and the elevation of standards of hygiene and sanitation, interfere with the so-called normal balance of nature. Adaptation to a changing environment, no matter by what agencies the changes are brought about, continues to be the price of survival.

HOT-WEATHER HEALTH HAZARDS

New England, having had a full measure of hot weather during midspring, may now prepare for the expected heat of midsummer and the discomforts and dangers attendant on it. True to its tradition of protecting the health, the safety and the sacred honor of the citizens of the Commonwealth, the Massachusetts Department of Public Health has issued a list of hot-weather hazards, with the sage counsel that they be avoided wherever possible. The fact that some of them seem fairly obvious need not be held to the discredit of the warning; otherwise, intelligent persons will annually cook themselves to a crisp in the hot sun, nor ever seem the wiser.

Early on the list of such hazards, consequently, come overexposure to the solar rays; overexertion — which many persons avoid at all times, regardless of season; deep water for nonswimmers; and crowded highways, which would be less crowded if more drivers heeded this warning. Contact with poison ivy and similar plants should be avoided, according to these advices, a warning that might be made more specific by an identification of "similar plants." Forest fires, a menace whenever they may occur, are a peculiar liability of dry springs and autumns, but since more people are prowling the woods in the vacation season a warning against unguarded camp fires and the careless disposal of matches and cigarettes is not out of order.

Playgrounds should be supervised; insecticides and, categorically, other poisons, should be plainly marked and kept out of the reach of children; foods should be even more carefully refrigerated in hot than in cool weather.

These are the nine somewhat heterogeneous commandments issued by the Department. A tenth and particularly appropriate one might refer to the stings of insects, ranging from that of the mosquito, now largely of nuisance value, to the severe and sometimes dangerous attacks of the hymenopterous wasps, hornets and bees, which hurt most when they sit down.

Pustule Maligne, an Inaugural Essay for the Degree of Doctor of Medicine.

By Daniel Wadsworth Wainwright, of New York City. New York, 1855. Pp. 32. This is a tolerable essay for a thesis, but the author would have been much wiser if he had not printed it.

Boston M. & S. J., *June 28, 1855*

MASSACHUSETTS MEDICAL SOCIETY

COMPLAINT DEPARTMENT

When a fellow of the Society takes his pen in hand to lodge a complaint with the organization he is apt to write with savage gusto. Often his indignation arises from misunderstanding. Perhaps it will have some prophylactic effect if a few recurrent misunderstandings are reviewed.

Why doesn't the Society do something about Blue Cross-Blue Shield coverage for members?

It has, and it does. Blue Cross loses money every year on doctors and their families because of their greater utilization of its benefits. To give physicians' families complete coverage would require a special policy with higher-than-average premiums. If we insist, this can be done. Until then we must put up with not having our personal hernia operations or our children's tonsillectomies during the first year of our Blue Cross-Blue Shield contract and with payments for hospital room and board that fail to meet their actual cost.

Does not the Massachusetts Medical Society issue a noncancellable group insurance policy guaranteeing full protection against disability from accident or illness to all its members without regard to their previous state of health? Why then was my claim rejected and my policy cancelled?

(It is possible that this complainant read only the advertising literature of a well conducted sales campaign; members were repeatedly warned to read the contract rather than the promotional literature.)

The Society issues no insurance. The contract approved by the Committee on Insurance is written and sold by a strictly commercial insurance company established for the main reason of making a profit. The offer, made by it once only to original subscribers at the initial enrollment period, was to give some kind of coverage (not unlimited) to all qualified applicants. It was clearly stated that the policy was can-

cellable at the option of the company under certain definite conditions. The company cannot be held responsible for the purchaser's failure to read and understand these terms.

Why do you pay no attention to my repeated requests that you correct my mailing address?

Probably because the Society has been confused with the *Norfolk Medical News*, the *New England Journal of Medicine* or the Postgraduate Medical Institute, any one of which may have been notified, with no notice yet mailed to 22 Fenway.

We not only continue to welcome but solicit letters, telephone calls and personal visits to the offices of the Society. We hope to be able to answer and perhaps occasionally to anticipate questions.

ROBERT W. BUCK, M.D.
Secretary

DEATHS

GREEN — Robert M. Green, M. D., of Brookline, died on May 29. He was in his seventy-sixth year.

Dr. Green received his degree from Harvard Medical School in 1906. He was formerly editor of the *New England Journal of Medicine*, associate professor of applied anatomy at Harvard Medical School and surgeon in charge of gynecology and obstetrics at Boston City Hospital. He was a member of the New England Obstetrical and Gynecological Society.

He is survived by his widow, five daughters, four sons and twelve grandchildren.

PARK — Irving H. Park, M. D., of Brookline, died on May 30. He was in his forty-fourth year.

He is survived by his widow, two sons and one daughter.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

DISCONTINUANCE OF COMPLEMENT FIXATION FOR AMEBIASIS

Specimens for the complement-fixation test for amebiasis are occasionally received by the Diagnostic Laboratory for forwarding to the Communicable Disease Center. A communication has recently been received from the Center referring to the conflicting evidence about the reliability of the test for amebiasis. Although some workers have reported satisfactory results others have indicated unsatisfactory correlation between the outcome of the complement-fixation test and clinical amebiasis. The Communicable Disease Center therefore does not consider the test in its present form sufficiently reliable for a routine diagnostic procedure, and is discontinuing it, and specimens for this purpose should no longer be sent to the Diagnostic Laboratory.

TOXOPLASMOSIS TESTS ON ADULTS

The Diagnostic Laboratory occasionally receives specimens obtained from adults to be sent to the Communicable Disease Center for the dye test for toxoplasmosis. A communication has recently been received from the Center regarding conclusions of a conference on granulomatous uveitis sponsored by the Parasitology and Tropical Medicine Section of the National Institutes of Health in December, 1954. The conference concluded that knowledge on the subject is still insufficient for reliable interpretation of the serologic results on eye lesions in adults. In consequence, and because the test is difficult and expensive, the Center will continue its policy of not performing the dye test for toxoplasmosis on specimens obtained from adults.

Existing facilities will continue to be utilized in cases where the test can be of greatest assistance, as in congenital lesions. For such studies it is necessary to obtain specimens from *both* mother and child.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

ORTHOPEDIC CLINIC	DATE	CLINIC CONSULTANT
Gardner	July 5	Carter R. Rowe, M.D.
Haverhill	July 6	William T. Green, M.D.
Lynn*	July 11	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Salem	July 11	Paul W. Hugenberger, M.D.
Brockton	July 14	George W. Van Gorder, M.D.
Worcester	July 15	John W. O'Meara, M.D.
Pittsfield	July 20	Edward J. Coughlin, Jr., M.D.
Hyannis	July 28	Paul L. Norton, M.D.
Greenfield	Aug. 4	Charles L. Sturdevant, M.D.
Lowell	Aug. 5	Albert H. Brewster, M.D.
Fall River	Aug. 22	David S. Grice, M.D.
Springfield	Aug. 23	James D. Fisher, M.D.

RHEUMATIC-FEVER CLINIC	DATES
North Reading	July 5, 12, 19, 26
Fitchburg	July 6, 13, 20, 27

PLASTIC CLINIC	HELD	CONSULTANT
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

CORRESPONDENCE

WHENCE THE MAORIS

To the Editor: John H. Holmes, in his Medical Intelligence article, "Sergeant Pellens's Contribution," in the May 12 issue of the *Journal*, describes the Maoris as "an ancient Polynesian tribe that originated in and about the Hawaiian Islands."

Strong ethnologic, cultural, religious and linguistic evidence points to a common origin of all Polynesians from the Ganges valley in pre-Aryan times. By 500 A.D. they had reached the Malay archipelago and Indonesia. From here, two waves of migration burst over the Pacific like an island-hopping pandemic, and by 1000 A.D. most of Polynesia was populated by the invaders.

The Maoris came to New Zealand from Tahiti by way of Rarotonga and were established by 1350. All Polynesians

continued to look back to the west, where the souls of the dead returned, to the legendary land of their forefathers, Hawaiki, which is linguistically related to Java.

True, much of Polynesian history is conjecture, but aside from Kon-Tiki, the pressure of migration has always been to the east, south and north — never to the west. The Hawaiians marked the last hop eastward.

NICHOLAS G. DEMY, M.D.

Plainfield, New Jersey

RESOLUTION FROM MIDDLESEX SOUTH

To the Editor: The councilors of Middlesex South District Medical Society met during the evening of the annual meeting of the Society and passed unanimously the following resolution:

> Resolved that the councilors of Middlesex South District Medical Society be recorded as commending Dr. Curtis C. Tripp, President of the Massachusetts Medical Society, for his untiring effort and labor to bring order out of chaos in the relations between the medical profession and the Department of Public Welfare of the Commonwealth of Massachusetts and that a copy of this resolution be transmitted to Dr. Tripp by the Secretary.

DAVID C. DOW, M.D.
Secretary
Middlesex South District Medical Society
Cambridge, Massachusetts

ESOPHAGEAL OBSTRUCTION

To the Editor: Dr. Edward B. Benedict, in his excellent article, "Endoscopy," in the May 5 issue of the *Journal*, refers to a case of esophageal obstruction due to Serutan, reported by Melamed and Marck. I trust that it is not immodest for me to call attention to a similar case that I reported in the *Journal of the American Medical Association* (153:235, 1953). Our patient was a seventy-two-year-old man, and after twenty hours of trying vainly to get rid of the Serutan in the esophagus, he obtained prompt relief after a few swallows of liquid Taka-Diastase, which is a starch digestant.

So far as I know, this was the first case reported in which Taka-Diastase was used.

WINGATE M. JOHNSON, M.D.
Winston-Salem, North Carolina

SUSPENSION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held March 24, 1955, it was voted to suspend the registration of Dr. Thomas P. Beatty, of South Boston, Massachusetts.

ROBERT C. COCHRANE, M.D.
Secretary
State House
Boston

BOOK REVIEW

The Child, His Parents and the Nurse. By Florence G. Blake, R.D., M.A. 8°, cloth, 440 pp. Philadelphia: J. B. Lippincott Company, 1954. $5.00.

When a baby is born today, if he is well born, with good obstetric care, he is handed from the physician to the nurse; it is the nurse who brings the child to the mother for feeding, and it is the nurse who helps the young mother learn the many things she needs to know to give her baby good care. This is a very original book and one of the first of its kind. The foreword by Adrian H. VanderVeer, M.D., points out the special need for a book of this sort and indicates its value. It is very well organized and well written, and a vast amount of valuable information is included in these 440 pages.

Essentially, this book reports broadly on the nursing care of children. It is written by a graduate nurse who has specialized in the field of child care. She has had wide clinical and practical experience. It is readable as a volume in its own right and also valuable as a reference book. Beginning with the prenatal period, it emphasizes the importance of the early months and the first year of rapid growth. Especially valuable is the fifth chapter on development and care during the training period. The author's views are comprehensive and up-to-date, tempered by experience and humanitarian zeal that shines through the pages. Obviously, also, she has read a great deal and gives many references but they fit well into the text. In one way this book offers a practical course in the psychology of child development for the nurse, whether at the student or at the graduate level. Handsomely published, it closes with a valuable index of 30 pages.

MERRILL MOORE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Hypothyroidism: An essay on modern medicine. By Paul Starr, M.D., professor of medicine, University of Southern California School of Medicine. 8°, paper, 127 pp., with 25 figures and 27 tables. Springfield, Illinois: Charles C Thomas, 1954. $3.75. (*American Lecture Series* No. 211.)

The author presents a comprehensive summary of the present knowledge of hypothyroidism. The text is divided into two parts: etiology, classification and diagnosis; and clinical syndrome and treatment. There is a bibliography of 82 references.

An Introduction to Pathology. By G. Payling Wright, D.M., F.R.C.P., professor of pathology, Guy's Hospital Medical School, University of London. Second edition. 8°, cloth, 636 pp., with illustrations and tables. New York: Longmans Green and Company, 1954. $7.50.

This new edition of a British book has been revised, and two chapters on the basic features of hypersensitivity reactions and cell and tissue changes brought about by ionizing radiation have been added. The references are carried as footnotes on the appropriate pages. The pertinent literature is noted, and there are indexes of names and subjects. The publishing, which was done in Great Britain, is excellent.

Biochemistry and Human Metabolism. By Burnham S. Walker, M.D., Ph.D., professor of biochemistry, Boston University School of Medicine; William C. Boyd, Ph.D., professor of immunochemistry, Boston University School of Medicine; and Isaac Asimov, Ph.D., assistant professor of biochemistry, Boston University School of Medicine. With a foreword by John T. Edsall, M.D., professor of biologic chemistry, Harvard University. Second edition. 8°, cloth, 904 pp., with 30 figures and 49 tables. Baltimore: Williams and Wilkins, 1954. $10.00.

This new edition of a book first published in 1952 has been revised with the inclusion of new material and the complete rewriting of the chapter on proteins and starvation. The text is divided into five parts on structure, control, growth, metabolism and pathology. Three appendixes deal with colloids and colloid phenomena, isotopes and the principles of thermodynamics. There is a list of abbreviations and symbols and a good index.

Protozoology. By Richard R. Kudo, D.Sc., professor of zoology, University of Illinois. Fourth edition. 8°, cloth, 966 pp., with 326 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $10.75.

The first edition of this special book was published in 1931, and the last in 1950 as a reprint of the third edition of 1946. In this edition the text has been thoroughly revised. Extensive bibliographies are appended to the chapters, and the literature has been reviewed. There are indexes of authors and subjects. The book is recommended for all medical libraries and to all persons interested in the subject.

Modern Occupational Medicine. Edited by A. J. Fleming, M.Sc., M.D., assistant medical director, E. I. duPont de Nemours and Company; and C. A. D'Alonzo, M.D., special assistant, medical division, E. I. duPont de Nemours and Company; associate editor, J. A. Zapp, Phd. D., director, Haskell Laboratory for Toxicology and Industrial Medicine, E. I. duPont de Nemours and Company. 8°, cloth, 414 pp., with 32 tables and 44 figures. Philadelphia: Lea and Febiger, 1954. $10.00.

This is a collected work written by 20 persons from the duPont de Nemours Company. The material is divided into seven sections on organization, industrial preventive medicine, the physical environment and occupational health, services allied to occupational medicine, psychiatry, toxicology and acute poisoning. Short lists of references are appended to the chapters. The book should be in all collections on the subject.

Historical Review of British Obstetrics and Gynaecology. Edited by J. M. Munro Kerr, R. W. Johnstone and Miles H. Phillips. 8°, cloth, 420 pp., with 14 tables. London: E. and S. Livingstone, Limited, 1954. $6.75. (Distributed in the United States by Williams and Wilkins Company, Baltimore.)

This work by 19 contributors is divided into two main parts: obstetrics and gynecology. The first is dealt with in three fifty-year periods, with a supplemental part of 12 special articles. There are indexes of names and subjects. The publication is excellent, and the book should be in all medical-history collections.

The Thematic Apperception Test and The Children's Apperception Test in Clinical Use. By Leopold Bellak, M.D., with the assistance of Marjorie Bristol. 4°, cloth, 273 pp., with illustrations. New York: Grune and Stratton, 1954. $6.75.

The author discusses these two projective tests, in full. There is a bibliography of 115 titles.

Spezielle Röntgenologie der Lungentuberkulose. By Dr. Med. E. Haefliger, chief physician and director, Zürich Heilstätte Wald, and lecturer, Universität Zürich; with a foreword by Dr. Med. G. Mark. 4°, cloth, 322 pp., with 210 illustrations. Basel: Benno Schwabe and Company, 1954. Geb. Fr. 52. —. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

This special book on the roentgenology of pulmonary tuberculosis is based on an analysis of 210 cases. The pertinent literature has been noted, and there is a bibliography of 10 pages. There is a good index, and the publishing is excellent. The book should be in all collections on the subject.

Advances in Internal Medicine. Edited by William Dock, M.D., Long Island College of Medicine, Brooklyn; and I. Snapper, M.D., Beth-El Hospital, Brooklyn. Volume 6. 8°, cloth, 385 pp., with illustrations. Chicago: Year Book Publishers, Incorporated, 1954. $10.00.

This volume of an important set contains review articles on uropepsin, glucagon, diagnosis of cancer of internal organs by Papanicolaou technic, spatial vectorcardiography, L.E.-cell phenomenon, biopsy studies of the liver and kidney, thrombotic thrombocytopenic purpura, porphyria, diaphragmatic hernia and determination of insulin in the blood. The set should be in all medical libraries.

Clinical Interpretation of Laboratory Tests. By Raymond H. Goodale, M.D., pathologist, Worcester Hahnemann and Fairlawn hospitals and Worcester County Sanatorium, Worcester, Clinton Hospital, Clinton, and Harrington Memorial Hospital, Southbridge, and consulting pathologist, Veterans Administration Hospital, Rutland Heights, Massachusetts. Third edition. 8°, cloth, 720 pp., with 105 illustrations, 6 in color. Philadelphia: F. A. Davis Company, 1954. $7.50.

This new edition has been thoroughly revised, and much material has been added, including blood volume and coagulation, antistreptolysin in rheumatic fever, pancytopenia, afribrinogenemia, antithrombin in acute pancreatitis, serum mucoprotein in extrahepatic biliary obstruction, fecal lysozyme in ulcerative colitis and revision of the viruses and fluid and electrolyte balance. The text is divided into two parts: body fluids, excreta and functional tests; and diseases with associated laboratory findings. Lists of references are appended to the chapters; there is a good index, and the publishing is excellent.

Babcock's Principles and Practice of Surgery. Edited by Karl C. Jones, M.D., M.S. (Surg.), F.A.C.S., F.I.C.S., Department of Surgery, Temple University School of Medicine and Hospital, Philadelphia. Second edition. 4°, cloth, 1543 pp., with 1006 illustrations and 10 colored plates. Philadelphia: Lea and Febiger, 1954. $18.00.

This new edition of a standard surgery has been revised and brought up to date. It is the joint work of 56 contributors and covers the whole field of surgery, including the specialties. Lists of references are appended to the chapters, and there is a good index. This is the type of book, approximating a serial, that should be in all medical libraries.

The Pineal Gland: A review of the physiologic literature. By Julian I. Kitay and Mark D. Altschule. 8°, cloth, 280 pp., with 77 tables. Cambridge: Harvard University Press, 1954. $5.00. (Published for the Commonwealth Fund.)

The authors have summarized the existing knowledge concerning the physiology of the pineal gland and its clinical aspects. The text is divided into two parts on physiology and clinical correlations. The studies indicate that the gland has a function but that it cannot be defined at present. There is a bibliography of 1762 items divided into three parts: physiology; anatomy, embryology, and histology; and reviews. The monograph should be in all collections on physiology and endocrinology.

Spinal Epidural Analgesia. By P. R. Bromage, M.B., B.S. (Lond.), F.F.A.R.C.S., D.A., consultant anesthetist, Chichester Hospitals Group, Portsmouth Hospitals Group, Ministry of Pensions Hospital, Cosham, and visiting anesthetist, King Edward VII Sanatorium, Midhurst. 8°, cloth, 123 pp., with 41 illustrations. Baltimore: Williams and Wilkins, 1954. $3.75.

The author discusses his subject thoroughly. He has reviewed the literature, and lists of references are appended to the chapters. There are indexes of authors and subjects. The printing was done in Great Britain. The monograph should be in collections on anesthesia.

The Mechanism of Labour. By Erik Rydberg, M.D., professor of obstetrics and gynecology, University of Copenhagen. 8°, cloth, 180 pp., with 38 figures. Springfield, Illinois: Charles C Thomas, 1954. $4.75. (Publication No. 181, *American Lecture Series.*)

Professor Rydberg has made an extensive study, by means of models and roentgenography, of the mechanisms of labor

in the normal type of vertex presentation and concludes that the usual process may be ascribed to the shape of the fetal head. A bibliography is appended to the text. The monograph should be in all collections on obstetrics.

Emergencies in Medical Practice. Edited by C. Allan Birch, M.D., F.R.C.P., physician, Chase Farm Hospital, Enfield. Fourth edition. 8°, cloth, 610 pp., with 143 illustrations. 9 in color. London: E. and S. Livingstone, Limited, 1954. $7.00.

First published in 1948, this new edition, the joint work of 23 contributors, has been revised and brought up to date, and material added on drug addiction, anthrax and milliequivalents. The text is divided into 28 chapters and covers all types of emergencies. There is a good index, and the book is well published.

Modern Diagnosis and Treatment of the Minor Venereal Diseases. By Orlando Canizares, M.D., associate professor of clinical dermatology and syphilology, New York University Post-Graduate Medical School, and consultant, Veterans Administration Hospital, Bronx, New York, and United States Public Health Service Hospital, Staten Island, New York. 8°, paper, 131 pp., with 19 illustrations and 7 tables. Springfield, Illinois: Charles C Thomas, 1954. $3.75. (Publication No. 223, *American Lecture Series.*)

Dr. Canizares, in this monograph, deals with chancroid, granuloma inguinale and lymphogranuloma venereum in general practice. There is a bibliography of 6½ pages and an index.

Nerve Blocks: A manual of regional anesthesia for practitioners of medicine. By John Adriani, M.D., director, Department of Anesthesiology, Charity Hospital of Louisiana, professor of surgery, Tulane University of Louisiana School of Medicine, and associate clinical professor of surgery, Louisiana State University School of Medicine. 8°, cloth, 265 pp., with 168 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $6.50.

Originally, the material in this monograph appeared in the author's *Techniques of Anesthesia,* first published in 1946. The section has now been enlarged and completely revised to form a separate book. The text covers the various types of nerve block and their use for surgical, diagnostic and therapeutic purposes. The text is well illustrated, and there is a good index. The book should be in all collections on anesthesia and neurology.

Myocardial Infarction: Its clinical manifestations and treatment with anticoagulants. By Irving S. Wright, M.D., Charles D. Marple, M.D., and Dorothy Fahs Beck, Ph.D. 4°, cloth, 656 pp., with illustrations. New York: Grune and Stratton, 1954. $8.50. (Published for the American Heart Association.)

The authors have made a comprehensive study of all phases of myocardial infarction. There is a bibliography of 267 references, as well as a good index, and the publishing is excellent. The book is recommended for all collections on cardiology.

Retropubic Prostatectomy: For benign enlargement of the prostate gland. By Francis A. Beneventi, M.D., attending urologist, Oswald Swinney Lowsley Foundation, St. Clare's Hospital, attending urologist, New York Polyclinic Hospital and Medical School, and assistant urologist, James Buchanan Brady Foundation of the New York Hospital, New York City. 4°, cloth, 227 pp., with 73 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $11.00.

This semiatlas discusses the operation in detail. It deals with anatomy of the prostate and its enlargement, clinical manifestations, operative technics, management before and after operation, postoperative complications, osteitis pubis, and history and evaluation of 100 cases. The literature has been noted, and there is a bibliography of 3 quarto pages. There are indexes of names and subjects; the publishing is excellent.

Symposium on the Cardiac in Industry: Held under the auspices of Golden Clinic, Memorial General Hospital Association, Elkins, West Virginia, 1953. 8°, paper, 135 pp., with 5 tables. 1954. (No price.)

Eleven papers on various aspects of the person with cardiac disease in industry were read and discussed at this symposium.

Surgery of the Adrenal Glands. By William Wallace Scott, M.D., Ph.D., professor of urology, Johns Hopkins University School of Medicine, urologist-in-charge, Johns Hopkins Hospital, and director, James Buchanan Brady Urological Institute, Baltimore, Maryland; and Perry B. Hudson, M.D., assistant professor of urology, Columbia University College of Physicians and Surgeons, assistant urologist, Presbyterian Hospital, and assistant visiting urologist, Francis Delafield Hospital, New York City. 8°, paper, 150 pp., with 35 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $3.50. (Publication No. 227, *American Lecture Series.*)

The authors discuss the function of the adrenal cortex and surgery of adrenal tumors, excluding Cushing's syndrome. There is a chapter on bilateral adrenalectomy in the treatment of disseminated cancer of the breast and prostate. The literature is reviewed, and there is a bibliography of 157 titles, as well as indexes of authors and subjects.

NOTICES

COURSE IN LABORATORY DIAGNOSIS OF TUBERCULOSIS

A course in the laboratory diagnosis of tuberculosis will be offered by the Communicable Disease Center and the Division of Special Health Services, Public Health Service, at Chamblee, Georgia, November 14 through 25, 1955.

The course is open to all employed laboratory personnel who are approved by their state health officers. Laboratory directors and senior staff members may also apply. There are no tuition or laboratory fees. Reservations must be made well in advance. Application forms may be obtained from the Laboratory Training Services, Communicable Disease Center, Public Health Service, P. O. Box 185, Chamblee, Georgia.

SOCIETY MEETINGS AND CONFERENCES

JULY, AUGUST and SEPTEMBER. Beth Israel Hospital Course. Page 509, issue of March 24.
JULY 1–4. International College of Surgeons. Page 828, issue of May 12.
JULY 10–16. Congress of Nobel Prize Winners. Page 510, issue of March 24.
JULY 11–15. Symposium on Tuberculosis. Page 509, issue of March 24.
AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
AUGUST 30 and 31 and SEPTEMBER 1. New England Health Institute. Page 1010, issue of June 9.
OCTOBER 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.
OCTOBER 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.
OCTOBER 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.
NOVEMBER 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.
NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.
NOVEMBER 11 and 12. Inter-Society Council. Page 1056, issue of June 16.
NOVEMBER 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Notice above.
NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.
NOVEMBER 29–DECEMBER 2. Interim Session of the American Medical Association, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JUNE 30

THURSDAY, JUNE 30
*8:00–8:45 a.m. Case Presentations, Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

(Concluded on page xix)

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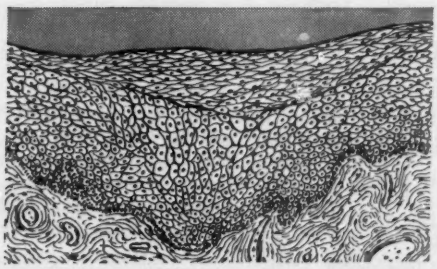
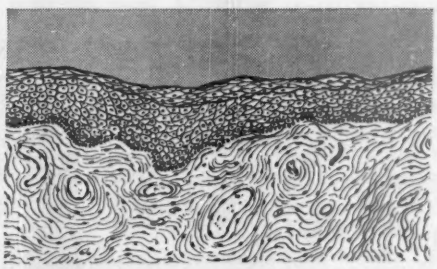
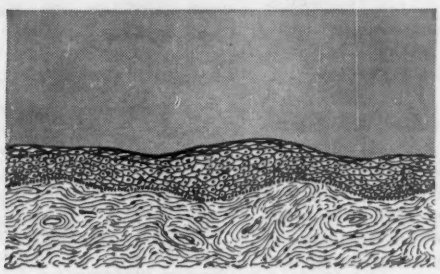


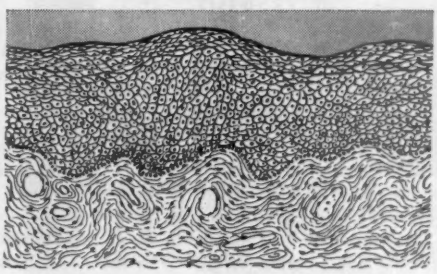
Adult vaginal epithelium maintained by estrogen activity.



During menopause, mucosa reverts to the infantile type.



Postmenopausal mucosa—thinning and atrophy of layers.



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*Sturnick, M. I., and Gargill, S. L.: New England J. Med. *247*:829 (Nov. 27) 1952.

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WANTED — Staff psychiatrists and physicians. Senior: Starting salary $8280. Assistant Physician: Starting salary $5880. Living quarters available. All modern therapies are given. Approved AMA. Easy commuting distance to Boston. Write: Peter B. Hagopian, M.D., Superintendent, Danvers State Hospital, Hathorne, Mass. B255-22-5t

3-ROOM SUITE suitable for doctor's office at 60 Brattle Street, (Harvard Square) Cambridge. Call TR 6-4473 after 5 p.m. or apply to superintendent. B256-22-3t

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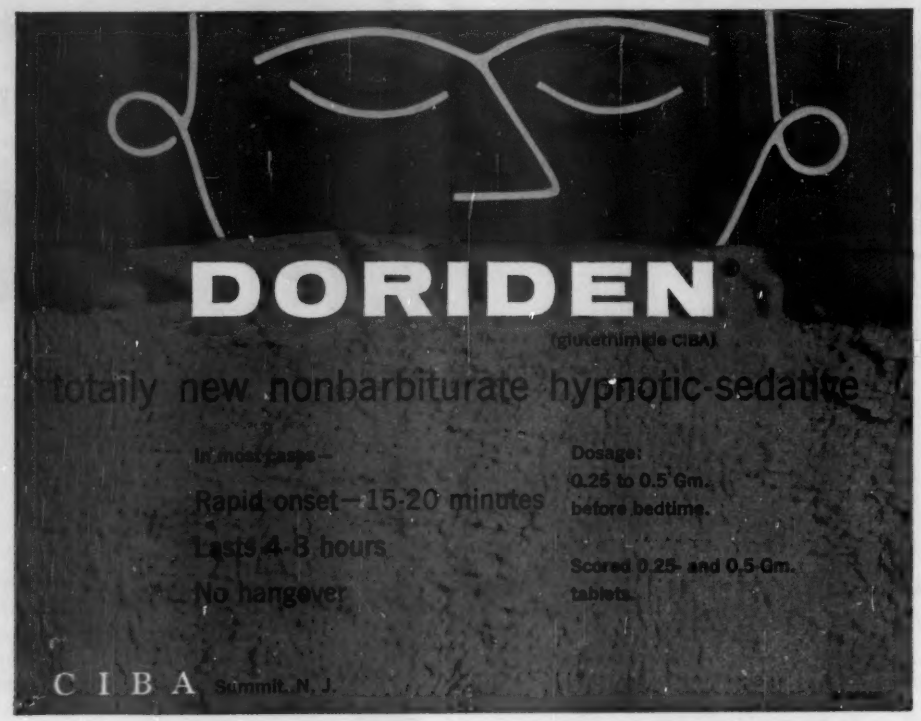

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(Concluded from page 1102)

*9:00–10:00 a.m. Grand Rounds. Russell Room, House of Good Samaritan.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Thoracic Conference. The Diagnosis and Treatment of Mitral Insufficiency. Dr. Dwight E. Harken. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, JULY 1
International College of Surgeons. Chatham Bars Inn, Chatham, Massachusetts.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic, Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, JULY 2
International College of Surgeons. Chatham Bars Inn, Chatham, Massachusetts.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

SUNDAY, JULY 3
International College of Surgeons. Chatham Bars Inn, Chatham, Massachusetts.

MONDAY, JULY 4
International College of Surgeons. Chatham Bars Inn, Chatham, Massachusetts.

TUESDAY, JULY 5
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic (Cafeteria), Peter Bent Brigham Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, JULY 6
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.

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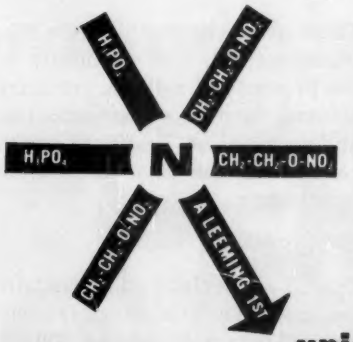

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1. Piper, C. E., and Nicklas, F. W.: Indust. Med. 23:510, 1954.

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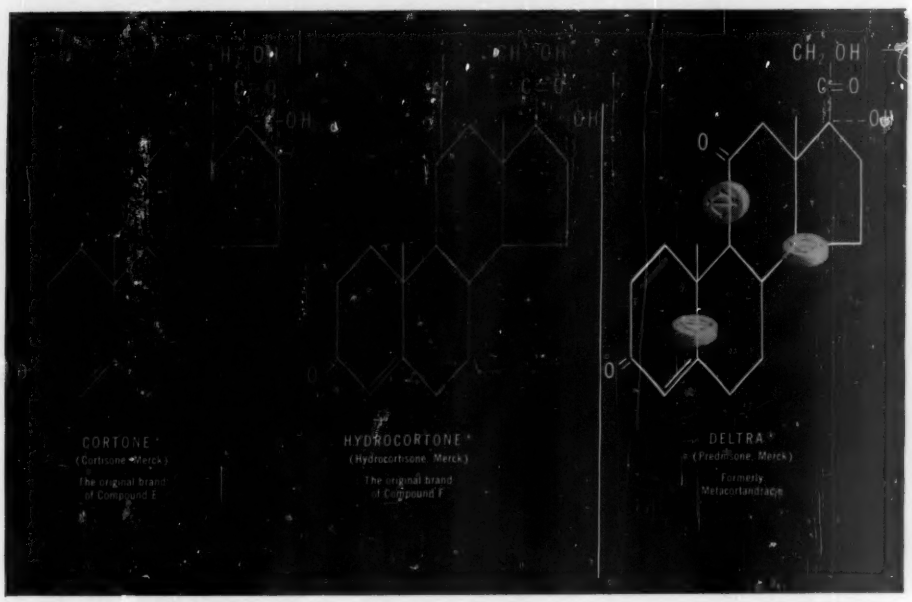

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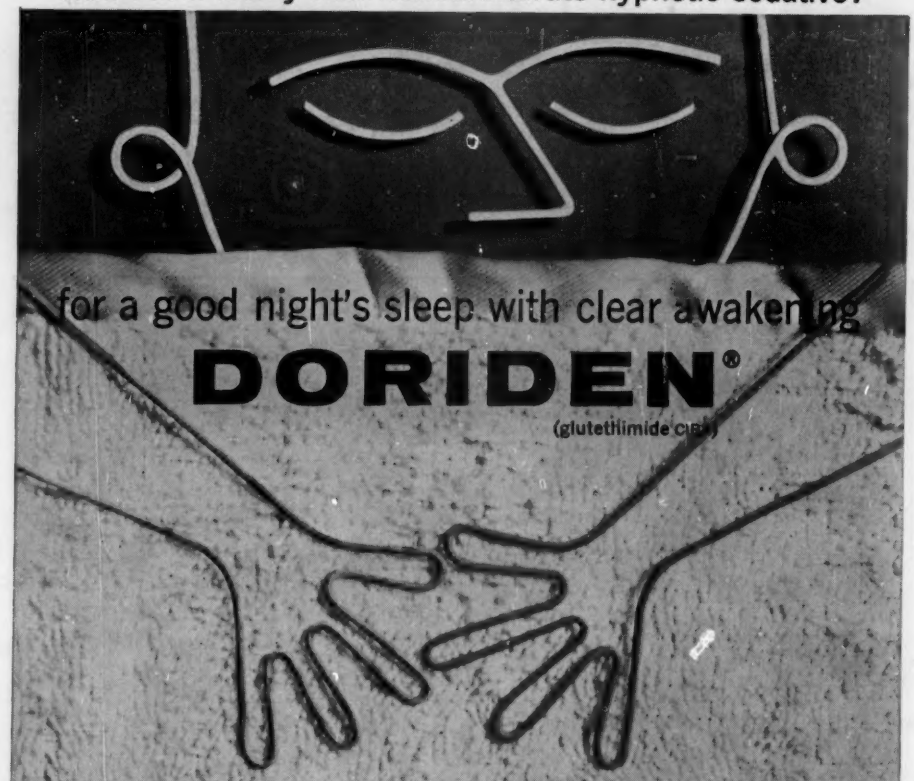

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